TRADE SECRET

Study Title

H-25435: Repeated-Dose Dermal Toxicity
28-Day Study in Male Rats

TEST GUIDELINES: U.S. EPA Health Effects Test Guidelines
OPPTS 870.3200 (1998)

OECD Guidelines for Testing of Chemicals
Section 4: Health Effects, Number 410 (1981)

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STUDY COMPLETED ON: September 3, 2003

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
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LABORATORY PROJECT ID: DuPont-11574

WORK REQUEST NUMBER: [redacted]

SERVICE CODE NUMBER: [redacted]

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

This study was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are consistent with the OECD Principles of Good Laboratory Practice (as revised in 1997) published in ENV/MC/CHEM(98) except for the item documented below. The item listed does not impact the validity of the study.

Test substance characterization and stability analyses were performed at Regional Analytical Services (RAS), Deepwater, New Jersey. None of the aforementioned analyses were performed under Good Laboratory Practice Standards; however, the analyses were conducted in compliance with ISO9002 regulations. All of the analyses are considered valid and sufficient for the purposes of this study.

Applicant / Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Director: Carol Finlay 3-Sept-2003
Carol Finlay, B.A. Date
Staff Toxicologist

Applicant / Sponsor: _____ _____
DuPont Representative Date

Company Sanitized. Does not contain TSCA CBI

QUALITY ASSURANCE STATEMENT

Haskell Sample Number(s):

25435

Dates of Inspections:

Protocol:	October 21, 2002
Conduct:	November 12, 2003
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	March 5, 2003
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	March 3, 2003
	March 17-18, 2003
	July 16, 17, 18, 21, 2003

Dates Findings Reported to:

Study Director:	October 21, 2002
	February 26, 2003
	March 3, 2003
	March 5, 2003
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Management:	October 21, 2002
	February 26, 2003
	March 3, 2003
	March 5, 2003
	March 20, 2003
	August 25, 2003

Reported by: Denise M. Janney 3-September-2003
Denise M. Janney Date
Quality Assurance Auditor

Company Sanitized. Does not contain TSCA CBI

CERTIFICATION

We, the undersigned, declare that this report provides an accurate evaluation of the data obtained from this study.

Clinical Pathology Evaluation by: _____ 2-Sept-2003
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Issued by Study Director: _____ 3 Sept 2003
Carol Finlay, B.A. Date
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STUDY INFORMATION

Substance Tested: [redacted]

Synonyms/Codes: [redacted]

- H-25435

[redacted]

Haskell Number: 25435

Composition: [redacted]

Known Impurities: [redacted]

Sponsor: E. I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Study Initiated/Completed: October 25, 2002 / (see report cover page)

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SUMMARY

The objective of this study was to determine the potential toxicity of H-25435 following repeated dermal exposure. The test substance was applied to the shaved, intact skin of male Crl:CD®(SD)IGS BR rats for 6 hours/day for 28 consecutive days. Three groups of 10 male rats were treated dermally with 10, 100, and 1000 mg/kg/day H-25435. A control group of 10 male rats was similarly treated with deionized water. The rats were observed for mortality, clinical signs, dermal effects, and body weight effects during the study. Food consumption was determined weekly during the study. Blood samples for total fluorine were collected on test days -4, 3, 9, and 21. Blood and urine samples were collected for clinical pathology prior to sacrifice on day 29. All rats underwent necropsy for gross and microscopic pathological evaluation.

There were no effects on body weight, food consumption, food efficiency, or mortality at any dosage. No clinical signs attributable to systemic toxicity occurred. No dermal irritation was observed during the study.

Some fluorine was present in the day 21 blood from rats dosed with the test substance, indicating exposure to a fluoride-containing compound. This finding was considered to be treatment-related but not adverse.

Organ weights were not different in a dose response fashion in either incidence or severity. Gross observations and microscopic findings occur spontaneously in rats of this strain and age and were not present in a dose response fashion in either incidence or severity.

There were no adverse changes in hematology parameters. Aspartate and alanine aminotransferase activities were increased along with increased sorbitol dehydrogenase activities in rats treated at 1000 mg/kg/day. These increases were considered to be potentially adverse. Urine fluoride was increased in rats treated at 1000 mg/kg/day, indicating exposure to and metabolism of a fluoride-containing compound. This urine fluoride increase was considered to be treatment-related but not adverse.

Based on the presence of mildly increased liver enzymes at 1000 mg/kg/day, the no-observed effect level (NOEL)[a] for the dermal exposure of H-25435 under the conditions of this study was 100 mg/kg/day for male rats.

[a] The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the U.S. EPA (1985) and to the no-observable-adverse-effect level (NOAEL) as defined by the European Union (1994).

INTRODUCTION

The purpose of this study was to evaluate the toxicity of H-25435 in rats when administered dermally for 28 days. This study was intended to provide insight to the possible human health hazards associated with repeated dermal exposures to the test substance over a limited period of time.

A range-finding study was conducted to aid in dosage selection for the 28-day dermal study. Groups of 2 male rats received dermal applications of H-25435 at dosages of 10, 60, 500, or 1000 mg/kg for 6 hours for 4 consecutive days. No dermal irritation was observed, and no test substance-related clinical signs or body weight losses occurred. Based on the lack of toxicity observed in the range finding study, dosages of 0, 10, 100, and 1000 mg/kg/day were selected for the 28-day study.

STUDY DESIGN

Group	Number/Group	Dosage (mg/kg)
I	10	0
III	10	10
V	10	100
VII	10	1000

MATERIALS AND METHODS

A. Test Guidelines

Except as noted below, the study design complies with the following test guidleines:

- Office of Prevention, Pesticides and Toxic Substances (OPPTS) U.S. Environmental Protection Agency (EPA) (1998). OPPTS 870.3200 21/28-Day Dermal Toxicity. *Health Effects Test Guidelines.*
- Organisation for Economic Co-Operation and Development (OECD) (1981). 410 Repeated Dose Dermal Toxicity: 21/28-Day Study. *Guideline for Testing of Chemicals.*

Only male rats were treated. This exception did not affect the objectives or validity of the study because males are the more sensitive sex to the toxicological effects of fluorinated test substances such as H-25435.

B. Test Substance

The test substance, H-25435, was supplied by the sponsor as an amber brown liquid. The test substance appeared to be stable under the conditions of the study. No evidence of instability, such as a change in color or physical state, was observed.

All of the test substance administered was assumed to be available for absorption. For the purposes of this study, all toxic effects were reported as a function of the administered dosage.

C. Test Species

On October 15, 2002, 44 male Crl:CD®(SD)IGS BR rats, with an assigned birth date of September 2, 2002, were received from Charles River Laboratories, Inc., Raleigh, North Carolina.

The Crl:CD®(SD)IGS BR rat was selected because extensive background information is available from the literature, the supplier, and previous studies conducted at Haskell Laboratory. This strain is also considered suitable relative to hardiness and low incidence of spontaneous disease.

D. Animal Husbandry

1. Housing

Rats were housed singly in stainless steel, wire-mesh cages suspended above cage boards.

2. Environmental Conditions

Animal rooms were maintained at a temperature of 19-25°C and a relative humidity of 30-70%. Animal rooms were artificially illuminated (fluorescent light) on an approximate 12-hour light/dark cycle. Excursions outside of these ranges were of insufficient magnitude and/or duration to have adversely affected the validity of the study.

3. Feed and Water

Tap water was provided *ad libitum*. PMI® Nutrition International, LLC Certified Rodent LabDiet® 5002 meal was available *ad libitum* except when the rats were fasted.

4. Identification

Prior to assignment to groups, each rat was temporarily identified by a cage card affixed to the outside of its cage. After assignment to groups, each rat was assigned a unique 6-digit Haskell animal number and an individual cage identification number. The last 3 digits of the Haskell animal number were tattooed on the tail of each rat. The information on the cage labels included the Haskell animal number and the individual identification number assigned to each rat.

5. Health Monitoring Program

As specified in the Haskell Laboratory animal health and environmental monitoring program, the following procedures are performed periodically to ensure that contaminant levels are below those that would be expected to impact the scientific integrity of the study:

- Water samples are analyzed for total bacterial counts, and the presence of coliforms, lead, and other contaminants.
- Feed samples are analyzed for total bacterial, spore, and fungal counts.
- Samples from freshly washed cages and cage racks are analyzed to ensure adequate sanitation by the cagewashers.

Certified animal feed is used, guaranteed by the manufacturer to meet specified nutritional requirements and not to exceed stated maximum concentrations of key contaminants, including specified heavy metals, aflatoxin, chlorinated hydrocarbons, and organophosphates. The presence of these contaminants below the maximum concentration stated by the manufacturer would not be expected to impact the integrity of the study.

The animal health and environmental monitoring program is administered by the attending laboratory animal veterinarian. Evaluation of these data did not indicate any conditions that affected the validity of the study.

E. Pretest Period

Upon arrival at Haskell Laboratory, the rats were quarantined for 6 days. The rats were weighed 3 times and examined daily for any clinically apparent signs of disease or injury.

On the bases of acceptable body weight gains and clinical signs, the rats were released from quarantine on test day -8 by the laboratory animal veterinarian's designee.

F. Assignment to Groups and Study Start

Forty rats were selected for study use on the bases of adequate body weight gain, freedom from clinical signs of disease or injury, and a body weight within ± 20% of the mean. The selected rats were divided by computerized, stratified randomization into 4 groups of 10 rats, so that there were no statistically significant differences among group body weight means.

Dose administration with H-25435 began on test day 0 when the rats were approximately 8 weeks of age.

G. Test Substance Preparation and Administration

On the day prior to the first treatment, the fur of each rat was closely shaved to expose the skin from the back and trunk. On each day of treatment, the rats wore plastic collars during the

exposure period to prevent ingestion of the test substance and disruption of the wrappings. The area to be treated was marked on the back of each rat with a water-insoluble marker. The approximate total body surface area covered for the 0, 10, 100, and 1000 mg/kg/day groups was 1.2%, 0.1%, 0.3%, and 1.5%, respectively. The volume of neat test substance or vehicle was not sufficient to cover 10% of the total body surface area. The test substance was applied evenly and as thinly as possible to the test site. The test substance was covered with a 2-ply porous gauze dressing followed by successive layers of stretch gauze (no more than 8 layers) and self-adhesive bandage. Each day of dosing, the control rats received the same volume of deionized water as the high-dose treatment group. The rats were treated at approximately the same time each day.

Groups of 10 male rats were treated at dosages of 0, 10, 100, or 1000 mg of test substance per kg body weight. The rats were treated for 28 consecutive days. The amount of neat test substance needed to treat each rat was based on the most recently determined body weight measurement and the test substance density of 1150 mg/mL.

The exposure period was approximately 6 hours. After the exposure period, the collars and wrappings were removed and the test site was wiped with a wet paper towel and washed with warm tap water. The test site of each rat was then gently patted dry and the rat was returned to its cage. Control animals received the same washing technique as the treated animals.

The animals were reshaved as needed during the study to facilitate the evaluation of dermal effects. The entire area that was originally shaved (including the untreated control skin) was reshaved. The animals were shaved only after an evaluation.

H. Body Weights

All rats were weighed at 3-4 day intervals during the study.

I. Food Consumption and Food Efficiency

The amount of food consumed by each rat was determined once per week throughout the study. Individual food consumption was determined by weighing the amount of diet in each feeder at the beginning and end of the week and subtracting the final weight and the amount of spillage from the feeder during the week from the initial weight. From these measurements, mean daily food consumption was determined. From the food consumption and body weight data, mean daily food efficiency was calculated.

J. Mortality and Clinical Observations

The rats were checked twice daily for mortality and for signs of illness, injury, or abnormal behavior.

The rats were observed for clinical signs of toxicity and dermal effects after removal of the test substance. The Draize Scale was used to score skin irritation. Adjacent areas of untreated skin were used for comparison. The rats were also observed for clinical signs at each weighing.

K. Total Fluorine and Perfluorooctanoic Acid Level Evaluations

Blood was collected into EDTA tubes from the orbital sinus of the first 5 rats in each group on test days -4, 3, 9, and 21 approximately one hour after removal of the test substance. The blood was refrigerated. The total fluorine content of the day 21 blood samples was determined by using a Wickbold torch combustion method followed by analysis with a fluoride ion selective electrode. The remaining samples were not analyzed. Fluorine blood analysis was performed at Jackson Laboratory, Deepwater, New Jersey.

Additional blood was collected from the vena cava of all rats at necropsy into a tube containing EDTA. Plasma was prepared and stored frozen at -80°C to -20°C. Concentration of perfluorooctanoic acid (PFOA) will be determined. The results of the analysis will be presented in a supplemental report.

L. Clinical Pathology Evaluation

A clinical pathology evaluation was conducted on all rats 29 days after initiation of the study. The day before collection of samples for the clinical pathology evaluation, the animals were placed in metabolism cages. These animals were fasted overnight (approximately 16 hours) and urine was collected from each animal. Blood samples for hematology and clinical chemistry measurements were collected from the orbital sinus of each animal while the animal was under carbon dioxide anesthesia. Blood was collected from the *vena cava* and was placed in a serum tube, processed to serum, and frozen at -80°C. Bone marrow smears were prepared at sacrifice from all surviving animals. Bone marrow smears were stained with Wright's stain, but analysis was not necessary to support experimental findings.

1. Hematology

Blood samples were evaluated for quality by visual examination prior to analysis. Complete blood counts, including reticulocytes, were determined on a Bayer® Advia 120 hematology analyzer or determined from microscopic evaluation of the blood smear. Wright-stained blood smears from all animals were examined microscopically for confirmation of automated results and evaluation of cellular morphology. Blood smears, stained with new methylene blue, were prepared from each animal undergoing a hematology evaluation but were not needed for examination.

The following hematology parameters were determined:

red blood cell count
hemoglobin
hematocrit
red cell distribution width
absolute reticulocyte count
platelet count

mean corpuscular volume	white blood cell count
mean corpuscular hemoglobin	differential white blood cell count
mean corpuscular hemoglobin concentration	microscopic blood smear examination

2. Clinical Chemistry

Serum clinical chemistry parameters were determined on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Plasma fluoride concentrations were determined using a phi12 pH meter and a fluoride-selective electrode.

The following clinical chemistry parameters were determined:

aspartate aminotransferase	glucose
alanine aminotransferase	total protein
sorbitol dehydrogenase	albumin
alkaline phosphatase	globulin
total bilirubin	calcium
urea nitrogen	inorganic phosphorus
creatinine	sodium
cholesterol	potassium
triglycerides	chloride
	fluoride[a]

3. Urinalysis

Urine volume and appearance (quality, color, and clarity) were measured and evaluated visually, respectively. Urine constituents were semi-quantitatively measured on a Bayer Clinitek® Atlas™ Automated Urine Chemistry analyzer. Urine protein was measured on a Roche Diagnostics (BMC)/Hitachi® 717 clinical chemistry analyzer. Urine osmolality was determined using an Advanced Osmometer 3900. Urine fluoride concentrations were determined using a phi12 pH meter and a fluoride-selective electrode, and total urine fluorides were calculated (volume x concentration). Sediments from all urine specimens were evaluated microscopically.

The following urinalysis parameters were determined:

quality	ketone
color	bilirubin
clarity	blood
volume	urobilinogen
osmolality	fluoride[b]
pH	protein
glucose	microscopic urine sediment examination

[a] Fluoride determination was analyzed on EDTA plasma.

[b] Fluoride determination was analyzed from urine with EDTA added.

M. Anatomic Pathology Evaluations

Rats were fasted after 3 p.m. on the afternoon before their scheduled sacrifice. A final sacrifice was performed on the rats following the final clinical pathology evaluation. All rats sacrificed by design underwent a gross and microscopic evaluation. Rats were euthanatized by carbon dioxide anesthesia and exsanguination. The order of sacrifice was random among all treatment groups.

The following tissues were collected from the rats:

gross observations[a]
liver[b]
kidneys[b]
thyroid gland (after fixation)[b]
skin (treated and untreated)
teeth

a Gross observations made at necropsy for which histopathology was not appropriate (e.g., fluid, ruffled fur, and missing anatomic parts) was generally not collected.
b Organs weighed

All tissues were placed in an appropriate fixative.

The rats had the following organs weighed: liver, kidneys, and thyroid. Relative organ weights (percent of final body weight) were calculated. Final body weights determined just prior to necropsy were used in the assessment of organ weight changes.

Tissues collected from rats in the high-dose and control group were further processed to slides, stained with hematoxylin and eosin, and examined microscopically. Most gross lesions and any additional target organs from rats in the low- and intermediate-dosage groups were evaluated microscopically. Selected gross observations for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic tail dermatitis, calculus, and deformities of the teeth, toe, tail, or ear pinna) were saved, but were not processed for microscopic evaluation.

N. Statistical Analyses

Significance was judged at $p < 0.05$.

		Method of Statistical Analysis	
Parameter	Preliminary Test	If preliminary test is not significant	If preliminary test is significant
Body Weight Body Weight Gain Food Consumption Food Efficiency Organ Weight	Test for lack of trend[2]	Sequential application[3] of the Jonckheere-Terpstra trend test[4]	Preliminary tests for pairwise comparison
	OR[a]		
	Levene's test for homogeneity[5] and Shapiro-Wilk test[6] for normality[b]	One-way analysis of variance[7] followed with Dunnett's test[8,9,10]	Kruskal-Wallis test[11] followed with Dunn's test[12]
Clinical Pathology[d]	Levene's test for homogeneity[5] and Shapiro-Wilk test[6] for normality[b]	One-way analysis of variance[7] followed with Dunnett's test[8,9,10]	Kruskal-Wallis test[11] followed with Dunn's test[12]
Survival Incidence of Clinical Observations Incidence of Dermal Effects	None	Cochran-Armitage test for trend[7]c	

a Pairwise comparisons and associated preliminary tests were only conducted if the test for lack of trend was significant.

b If the Shapiro-Wilk test was not significant but Levene's test was significant, a robust version of Dunnett's test was used. If the Shapiro-Wilk test was significant, Kruskal-Wallis test was followed by Dunn's test.

c If the incidence was not significant, but a significant lack of fit occurred, then Fisher's Exact test[13] with a Bonferroni correction was used.

d When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

RESULTS AND DISCUSSION

In-Life Toxicology

A. Mean Body Weights and Body Weight Gains
(Tables 2-3, Figure 1, Appendix B)

No effects on body weights or body weight gains occurred in any group of rats dosed with the test substance, H-25435.

B. Food Consumption and Food Efficiency
(Tables 4-5, Appendix C)

No effects on food consumption or food efficiency occurred in any group of rats dosed with the test substance.

C. Clinical Observations, Dermal Evaluations, and Survival
(Tables 6-8, Appendices D-F)

No clinical signs resulting in systemic toxicity occurred. Red ocular discharge was observed in all rats during the study. Red nasal discharge and swollen face were observed in rats in all dose groups. These clinical signs are considered to be due to the wrapping/collar application procedure. Superficial wounds and hair loss were present in both treated and control animals and were not considered test substance-related. The observation of dark eye in one rat treated at 100 mg/kg was short in duration, was not observed in any other rats, and therefore is not considered to be test substance-related.

No dermal irritation was observed during the study.

No deaths occurred.

D. Blood Fluorine Analysis
(Appendix G)

There was some fluorine present in the day 21 blood from rats dosed with the test substance. This indicated exposure to a fluoride-containing compound and is considered to be treatment related but not adverse. Two rats treated at 10 mg/kg/day had fluorine levels below the limit of quantification (LOQ). The remaining 3 rats had levels ranging from 0.52 to 5.96 ppm. The rats treated at 100 mg/kg had levels of fluorine ranging from 0.54 to 0.78 ppm. Two rats treated at

1000 mg/kg/day had fluorine levels below the LOQ. The remaining 3 rats had levels ranging from 1.22 to 1.38 ppm. All values for the control rats were below the LOQ.

E. In-Life Conclusions

Under the conditions of this study, the no-observed-effect level for inlife parameters was 1000 mg/kg/day for male rats based on the absence of adverse effects.

Clinical Pathology Evaluations

A. Hematology
(Table 9, Appendix H)

There were no adverse changes in hematologic parameters in males. The following statistically significant changes in mean hematologic parameters were considered to be non-adverse or not related to exposure to the test substance:

- Mean red cell parameters (red cell count, hemoglobin, and hematocrit) were similarly decreased in males dosed with 10, 100, or 1000 mg/kg/day (statistically significant for red cell count at 10 mg/kg/day, and for hemoglobin and hematocrit at 100 and 1000 mg/kg/day). There was no dose-relationship to the changes, despite the 100-fold range of doses. There were no correlative changes in other red cell parameters (reticulocytes, indices, or morphology) that would be expected with processes that alter red cell mass. In addition, red cell mass parameters for the three dosed groups were similar to that of the control groups on a recent dermal study.[14] It is likely that the apparent decrements in red cell mass were due to higher than usual red cell mass in the control group, rather than a direct effect of the compound. Therefore, these changes were considered to be unrelated to treatment.

- Eosinophils were minimally increased in males dosed with 1000 mg/kg/day (147% of control group mean). Due to the consistency of change, this increase was likely to be due to treatment. There were no other alterations in leukocyte counts, and no correlative histologic changes. In addition, eosinophils counts of all individual rats dosed with 1000 mg/kg/day were within the range of the control group counts. Therefore, although this change was possibly related to treatment, it was considered to be non-adverse.

B. Clinical Chemistry
(Table 10, Appendix H)

Aspartate and alanine aminotransferase activities were minimally (aspartate aminotransferase) to mildly (alanine aminotransferase) increased in some males dosed with 100 or 1000 mg/kg/day. In these groups, mean activities were statistically significant, and were 133-144% of control for aspartate aminotransferase, and 200-222% of control for alanine aminotransferase. In individual

affected rats, generally activities of both enzymes were elevated. Sorbitol dehydrogenase was also increased in affected rats in both groups, although mean activities were not statistically different from the control mean. The presence of increased transaminases and sorbitol dehydrogenase indicates hepatocellular injury. Histologically, there were no alterations in the liver. Due to the magnitude of the change, this effect was considered to be potentially adverse.

There were no other adverse changes in clinical chemistry parameters. The following statistically significant changes in mean clinical chemistry parameters were considered to be non-adverse or not related to exposure to the test substance:

- Alkaline phosphatase was minimally increased in males dosed with 1000 mg/kg/day (mean was 136% of control group mean). This change was possibly related to treatment. However, the magnitude of change was very small. In addition, there were no alterations in correlative clinical or anatomic pathology parameters. Increased alkaline phosphatase activity did not occur in the same rats that had increased transaminase and sorbitol dehydrogenase activities. Therefore, although this change was possibly related to treatment, it was considered to be non-adverse.

- Bilirubin was statistically and minimally increased in males dosed with 1000 mg/kg/day (133% of control group mean). Mean and individual bilirubin concentrations for this group (mean: 0.12 mg/dL, individual values: <0.10 to 0.16 mg/dL) were well within the historical age-matched control range (control mean range: 0.09-0.29 mg/dL; range of individual animals: 0.07-0.33 mg/dL). Based on individual rat data compared to the control and other treated groups, this change was unlikely to be related to treatment. Regardless, the magnitude of change was very small, and non-adverse.

- Cholesterol was minimally increased in males dosed with 10, 100, or 1000 mg/kg/day. Although this change may have been related to treatment, the magnitude of change was very small, and was not expected to result in adverse events. Therefore, this change was considered to be non-adverse.

- Triglycerides were minimally increased in males dosed with 10, 100, or 1000 mg/kg/day (147%, 150%, and 187% of control group means; statistically significant only at 1000 mg/kg/day). Increased triglycerides were likely to be treatment-related. However, the magnitude of change was very small, and was not expected to result in adverse events. Therefore, this change was considered to be non-adverse.

The following statistically significant change in mean clinical chemistry parameters was considered to be non-adverse because it was unrelated to dose:

- Minimally decreased albumin in males dosed with 100 mg/kg/day

C. Urinalyses

(Table 11, Appendix H)

There were no adverse changes in urinalysis parameters. The following statistically significant changes in mean urinalysis parameters were considered to be non-adverse:

- Urine osmolality was mildly decreased (62% of control group means) in males dosed with 1000 mg/kg/day. This was associated with an appropriate tendency (not statistically significant) towards minimally higher urine volumes in this group. There were no alterations in other renal parameters on this study. The presence of decreased osmolality with increased urine volume, in the absence of other changes in renal parameters, has no toxicologic significance. Therefore, this change was considered to be non-adverse.

- Urine protein concentration was decreased in males dosed with 1000 mg/kg/day. Decreases in urine protein concentration were secondary to increased urine volume. In addition, decreases in urine protein have no toxicologic significance. Therefore, this change was considered to be non-adverse.

D. Urine and Plasma Fluoride

There was no effect of treatment on plasma fluoride concentration.

Urine fluoride (total fluoride excreted overnight) was increased in males dosed with 1000 mg/kg/day (Text Table I). Increased urine fluoride indicates exposure to and metabolism of a fluoride-containing compound.

Text Table I: Mean urine fluoride for males

	Dose (mg/kg/day)			
Parameter (units)	0	10	100	1000
UFLU (µg)	14.8	17.4	19.2	***33.9***
% of control mean	NA	118%	130%	***229%***

Statistical significance is indicated by bold italicized type

E. Clinical Pathology Conclusions

In conclusion, dermal dosing of male rats with 1000 mg/kg/day resulted in increased aspartate and alanine aminotransferase activities, along with increased sorbitol dehydrogenase activities, in some rats. This change was considered to be potentially adverse. Urine fluoride was increased in males dosed with 1000 mg/kg/day; this change indicated exposure to and metabolism of a fluoride-containing compound, and was considered to be treatment-related but non-adverse.

Therefore, under the conditions of this study and for the clinical pathology parameters measured, the no-observed-effect level was 100 mg/kg/day for male rats, based on the presence of mildly increased liver enzymes at 1000 mg/kg/day.

Anatomic Pathology Evaluations

A. Mortality

There were no early deaths.

B. Organ Weights
(Table 12, Appendix I)

Organ weights were not different in a dose response fashion in either incidence or severity.

C. Gross Observations
(Table 13, Appendix J)

All gross observations noted are known to occur spontaneously in rats of this strain and age and were not present in a dose response fashion in either incidence or severity.

D. Microscopic Findings
(Table 14, Appendix J)

All microscopic observations noted are known to occur spontaneously in rats of this strain and age and were not present in a dose response fashion in either incidence or severity.

E. Anatomic Pathology Conclusions

Under the conditions of this study, the no-observed-effect level for pathology was 1000 mg/kg/day.

CONCLUSIONS

No deaths occurred during the study. No adverse test substance-related effects on body weight, food consumption, food efficiency, clinical signs, or dermal irritation were seen in male rats that received 28 applications of H-25435 applied daily to the shaved skin. Organ weight differences, gross observations, and microscopic findings were considered to occur spontaneously in rats and/or were not present in a dose response fashion. There were no adverse changes in hematology or urinalysis parameters.

Dermal administration of H-25435 resulted in increased aspartate and alanine aminotransferase activities along with increased sorbitol dehydrogenase activities at 1000 mg/kg/day.

The no-observed-effect level (NOEL)[a] was 100 mg/kg/day based on the presence of mildly increased liver enzymes at 1000 mg/kg/day.

RECORDS AND SAMPLE STORAGE

All data and records for analytical characterizations conducted by the sponsor will be retained by the sponsor. Laboratory-specific or site-specific raw data, such as personnel files and equipment records will be retained by the facility where the work was done.

A sample of the test substance will be collected for archive purposes and retained at Haskell Laboratory, Newark, Delaware. Specimens (if applicable), raw data, and the final report will be retained at Haskell Laboratory, Newark, Delaware or at Iron Mountain Records Management, Wilmington, Delaware.

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[a] The NOEL for this study is defined as the highest dose at which toxicologically important effects attributable to the test substance were not detected. Thus, for this study, the NOEL is equivalent to the NOEL as defined by the United States Environmental Protection Agency [15] and to the no-observed-adverse-effect level (NOAEL) as defined by the European Union.[16]

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TABLES

TABLES

EXPLANATORY NOTES

ABBREVIATIONS:

Summary of Hematology Values

RBC - red blood cell count
HGB - hemoglobin
HCT - hematocrit
MCV - mean corpuscular volume
MCH - mean corpuscular hemoglobin
MCHC - mean corpuscular hemoglobin concentration
RDW - red cell distribution width
ARET - absolute reticulocyte count
PLT - platelet count
WBC - white blood cell count
ANEU - absolute neutrophil (all forms)
ALYM - absolute lymphocyte
AMON - absolute monocyte
AEOS - absolute eosinophil
ABAS - absolute basophil
ALUC - absolute large unstained cell

Summary of Clinical Chemistry Values

AST - aspartate aminotransferase
ALT - alanine aminotransferase
SDH - sorbitol dehydrogenase
ALKP - alkaline phosphatase
BILI - total bilirubin
BUN - urea nitrogen
CREA - creatinine
CHOL - cholesterol
TRIG - triglycerides
GLUC - glucose
TP - total protein
ALB - albumin
GLOB - globulin
CALC - calcium
IPHS - inorganic phosphorous
NA - sodium
K - potassium
CL - chloride
PFLU - plasma fluoride

TABLES

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Summary of Urinalysis Values

VOL - volume
UOSM - urine osmolality
pH - the logarithm of the reciprocal of the hydrogen ion concentration
URO - urobilinogen
UFLU - urine fluoride
UMTP - urine protein

NOTES:

Summary of Hematology Values
Summary of Clinical Chemistry Values
Summary of Urinalysis Values
When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

TABLE 1

MEAN DAILY APPLIED DOSE VOLUMES FOR MALE RATS (µL)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY0	242.2 16.6(10)	2.5 0.1(10)	24.4 1.0(10)	247.6 10.6(10)
DAY1	242.2 16.6(10)	2.5 0.1(10)	24.4 1.0(10)	247.6 10.6(10)
DAY2	242.2 16.6(10)	2.5 0.1(10)	24.4 1.0(10)	247.6 10.6(10)
DAY3	256.1 19.9(10)	2.6 0.1(10)	25.7 1.0(10)	260.3 13.2(10)
DAY4	256.1 19.9(10)	2.6 0.1(10)	25.7 1.0(10)	260.3 13.2(10)
DAY5	256.1 19.9(10)	2.6 0.1(10)	25.7 1.0(10)	260.3 13.2(10)
DAY6	256.1 19.9(10)	2.6 0.1(10)	25.7 1.0(10)	260.3 13.2(10)
DAY7	267.5 22.4(10)	2.7 0.2(10)	26.5 1.0(10)	270.5 14.1(10)
DAY8	267.5 22.4(10)	2.7 0.2(10)	26.5 1.0(10)	270.5 14.1(10)
DAY9	267.5 22.4(10)	2.7 0.2(10)	26.5 1.0(10)	270.5 14.1(10)
DAY10	280.9 23.8(10)	2.9 0.2(10)	27.4 1.1(10)	283.2 14.8(10)

TABLE 1 (CONTINUED)

MEAN DAILY APPLIED DOSE VOLUMES FOR MALE RATS (µL)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY11	280.9 23.8(10)	2.9 0.2(10)	27.4 1.1(10)	283.2 14.8(10)
DAY12	280.9 23.8(10)	2.9 0.2(10)	27.4 1.1(10)	283.2 14.8(10)
DAY13	280.9 23.8(10)	2.9 0.2(10)	27.4 1.1(10)	283.2 14.8(10)
DAY14	290.8 23.6(10)	3.0 0.2(10)	28.1 1.3(10)	293.4 15.2(10)
DAY15	290.8 23.6(10)	3.0 0.2(10)	28.1 1.3(10)	293.4 15.2(10)
DAY16	290.8 23.6(10)	3.0 0.2(10)	28.1 1.3(10)	293.4 15.2(10)
DAY17	300.5 24.8(10)	3.1 0.2(10)	29.0 1.4(10)	302.1 18.9(10)
DAY18	300.5 24.8(10)	3.1 0.2(10)	29.0 1.4(10)	302.1 18.9(10)
DAY19	300.5 24.8(10)	3.1 0.2(10)	29.0 1.4(10)	302.1 18.9(10)
DAY20	300.5 24.8(10)	3.1 0.2(10)	29.0 1.4(10)	302.1 18.9(10)
DAY21	309.2 23.1(10)	3.2 0.2(10)	30.0 1.4(10)	314.1 20.3(10)

TABLE 1 (CONTINUED)

MEAN DAILY APPLIED DOSE VOLUMES FOR MALE RATS (µL)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY22	309.2 23.1(10)	3.2 0.2(10)	30.0 1.4(10)	314.1 20.3(10)
DAY23	309.2 23.1(10)	3.2 0.2(10)	30.0 1.4(10)	314.1 20.3(10)
DAY24	313.1 26.4(10)	3.3 0.2(10)	30.7 1.6(10)	321.3 21.5(10)
DAY25	313.1 26.4(10)	3.3 0.2(10)	30.7 1.6(10)	321.3 21.5(10)
DAY26	313.1 26.4(10)	3.3 0.2(10)	30.7 1.6(10)	321.3 21.5(10)
DAY27	313.1 26.4(10)	3.3 0.2(10)	30.7 1.6(10)	321.3 21.5(10)
DAY28	320.4 26.2(10)	3.3 0.3(10)	31.4 1.8(10)	331.4 20.7(10)

Data summarized as: Mean
Standard Deviation (n)

TABLE 2

MEAN BODY WEIGHTS OF MALE RATS (g)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY0	278.6 19.1(10)	283.3 15.4(10)	280.4 11.0(10)	284.7 12.2(10)
DAY3	294.5 22.9(10)	297.6 17.0(10)	295.1 11.3(10)	299.4 15.2(10)
DAY7	307.7 25.8(10)	313.3 19.8(10)	304.6 11.7(10)	311.1 16.2(10)
DAY10	323.0 27.3(10)	331.3 20.6(10)	315.4 13.2(10)	325.7 17.0(10)
DAY14	334.4 27.1(10)	345.5 22.9(10)	323.6 15.4(10)	337.4 17.4(10)
DAY17	345.6 28.6(10)	356.8 25.5(10)	333.1 16.4(10)	347.4 21.7(10)
DAY21	355.6 26.6(10)	370.6 28.4(10)	345.1 16.3(10)	361.2 23.3(10)
DAY24	360.1 30.4(10)	378.4 28.1(10)	352.8 18.3(10)	369.5 24.8(10)
DAY28	368.4 30.1(10)	384.8 30.3(10)	360.7 20.3(10)	381.1 23.8(10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 3

MEAN BODY WEIGHT GAINS OF MALE RATS (g)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY0-DAY3	15.9 7.2(10)	14.3 5.6(10)	14.6 6.5(10)	14.7 9.0(10)
DAY3-DAY7	13.2 5.2(10)	15.8 5.5(10)	9.6 5.4(10)	11.7 4.5(10)
DAY7-DAY10	15.3 4.2(10)	17.9 5.9(10)	10.7 6.1(10)	14.6 4.7(10)
DAY10-DAY14	11.4 5.8(10)	14.3 4.9(10)	8.3 4.4(10)	11.7 7.0(10)
DAY14-DAY17	11.2 5.5(10)	11.2 3.7(10)	9.5 6.6(10)	10.0 9.9(10)
DAY17-DAY21	10.0 7.1(10)	13.9 5.8(10)	12.0 6.9(10)	13.8 6.6(10)
DAY21-DAY24	4.5 6.5(10)	7.8 5.2(10)	7.6 7.6(10)	8.3 7.3(10)
DAY24-DAY28	8.3 7.5(10)	6.5 9.4(10)	7.9 9.6(10)	11.6 6.7(10)
DAY0-DAY 28	89.9 15.5(10)	101.6 23.1(10)	80.3 17.5(10)	96.5 21.1(10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 4

MEAN DAILY FOOD CONSUMPTION BY MALE RATS (g/day)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY0-DAY7	26.7 2.1(10)	26.2 1.6(10)	25.6 1.6(10)	26.1 2.1(10)
DAY7-DAY14	26.6 1.7(10)	26.9 1.8(10)	25.6 1.1(10)	27.1 1.6(10)
DAY14-DAY21	26.4 1.4(10)	26.9 1.6(10)	26.1 1.0(10)	27.2 1.9(10)
DAY21-DAY28	27.3 0.9(10)	27.5 1.3(10)	27.2 1.3(10)	27.5 1.1(10)
DAY0-DAY28	26.7 1.3(10)	26.9 1.3(10)	26.1 0.9(10)	27.0 1.5(10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 5

MEAN DAILY FOOD EFFICIENCY OF MALE RATS
(g body weight gain/g food consumed)

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
DAY0-DAY7	0.152 0.055 (10)	0.163 0.034 (10)	0.135 0.034 (10)	0.141 0.050 (10)
DAY7-DAY14	0.143 0.027 (10)	0.169 0.041 (10)	0.106 0.056 (10)	0.139 0.039 (10)
DAY14-DAY21	0.115 0.040 (10)	0.132 0.034 (10)	0.117 0.047 (10)	0.123 0.053 (10)
DAY21-DAY28	0.067 0.039 (10)	0.073 0.064 (10)	0.081 0.048 (10)	0.103 0.036 (10)
DAY0-DAY28	0.120 0.017 (10)	0.134 0.027 (10)	0.109 0.022 (10)	0.127 0.023 (10)

Data summarized as: Mean
Standard Deviation (n)

There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 6

SUMMARY OF CLINICAL OBSERVATIONS IN MALE RATS

Group	I	III	V	VII
Dosage(mg/kg)	0	10	100	1000
Animal Count	10	10	10	10
Discharge				
Eye right				
Incidence	0	0	0	1 (10%)
Mean onset (Days)				29
Nose				
Incidence	0	2 (20%)	0	0
Mean onset (Days)		3		
Hair Loss				
Incidence	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Mean onset (Days)	21	28	22	9
Wound				
Superficial				
Incidence	2 (20%)	1 (10%)	1 (10%)	2 (20%)
Mean onset (Days)	19	18	18	9

Incidence - The number of animals for which an observation was recorded.
Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test.

TABLE 7

SUMMARY OF CLINICAL OBSERVATIONS – POST DOSING IN MALE RATS

Group	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
Animal Count	10	10	10	10
Eye Observations				
Dark				
Incidence	0	0	1 (10%)	0 (0%)
Mean onset (Days)			4	
Discharge				
Eye				
Incidence	10 (100%)	10 (100%)	10 (100%)	10 (100%)
Mean onset (Days)	5	5	7	8
Nose				
Incidence	1 (10%)	2 (20%)	1 (10%)	1 (10%)
Mean onset (Days)	3	2	3	6
Hair Loss				
Incidence	1 (10%)	1 (10%)	1 (10%)	2 (20%)
Mean onset (Days)	21	27	13	9
Wound				
Superficial				
Incidence	2 (20%)	1 (10%)	1 (10%)	2 (20%)
Mean onset (Days)	19	15	17	10

TABLE 7 (CONTINUED)

SUMMARY OF CLINICAL OBSERVATIONS – POST DOSING IN MALE RATS

Group	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
Animal Count	10	10	10	10
Swollen Observations				
Face				
Incidence	4 (40%)	1 (10%)	2 (20%)	2 (20%)
Mean onset (Days)	1	14	2	0

Incidence - The number of animals for which an observation was recorded.
Mean onset (Days) - The mean of the first test day an observation was recorded for that group.

There were no statistically significant differences at $p < 0.05$ by Cochran-Armitage trend test.

TABLE 8

PERCENT SURVIVAL OF MALE RATS

Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
Days on Test				
0	100	100	100	100
7	100	100	100	100
14	100	100	100	100
21	100	100	100	100
28	100	100	100	100
Number at study start	10	10	10	10
Alive on test day 28	10	10	10	10

Percent Survival = (Number of rats alive/Number of rats at risk)*100
Number of rats at risk = Number at study start.

There were no statistically significant decreases in survival.

TABLE 9

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
RBC ($x10^6/\mu L$)				
DAY 29	8.32	7.95*[a]	7.95[a]	8.01
	0.34(10)	0.36(10)	0.36(10)	0.27(10)
HGB (g/dL)				
DAY 29	16.3	15.9	15.6*	15.6*
	0.6(10)	0.6(10)	0.6(10)	0.3(10)
HCT (%)				
DAY 29	48.2	46.6	46.0*	45.8*
	1.8(10)	1.1(10)	1.8(10)	0.9(10)
MCV (fl)				
DAY 29	58.0	58.7	57.8	57.1
	1.8(10)	1.8(10)	1.4(10)	1.8(10)
MCH (pg)				
DAY 29	19.6	20.0	19.6	19.4
	0.5(10)	0.6(10)	0.6(10)	0.5(10)
MCHC (g/dL)				
DAY 29	33.8	34.0	34.0	34.0
	0.3(10)	0.6(10)	0.6(10)	0.4(10)
RDW (%)				
DAY 29	11.0	11.1	10.9	11.1
	0.5(10)	0.4(10)	0.3(10)	0.5(10)
ARET ($x10^3/\mu L$)				
DAY 29	177.4	190.5	172.6	185.1
	49.9(10)	42.2(10)	54.5(10)	35.5(10)
PLT ($x10^3/\mu L$)				
DAY 29	1186	1277	1326	1265
	115(9)	125(8)	157(10)	175(8)
WBC ($x10^3/\mu L$)				
DAY 29	12.05	12.17	12.85	14.66
	3.27(10)	3.04(10)	2.15(10)	2.42(10)
ANEU ($x10^3/\mu L$)				
DAY 29	1.70	1.59	1.37	2.00
	0.91(10)	0.57(10)	0.21(10)	0.72(10)
ALYM ($x10^3/\mu L$)				
DAY 29	9.61	9.85	10.72	11.69
	2.32(10)	2.77(10)	2.14(10)	1.82(10)

TABLE 9 (Continued)

SUMMARY OF HEMATOLOGY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
AMON ($x10^3/\mu L$)				
DAY 29	0.31	0.27	0.31	0.41
	0.12(10)	0.06(10)	0.07(10)	0.13(10)
AEOS ($x10^3/\mu L$)				
DAY 29	0.17	0.21	0.19	0.25@
	0.07(10)	0.09(10)	0.06(10)	0.05(10)
ABAS ($x10^3/\mu L$)				
DAY 29	0.12	0.11	0.09	0.14
	0.04(10)	0.03(10)	0.04(10)	0.06(10)
ALUC ($x10^3/\mu L$)				
DAY 29	0.14	0.14	0.17	0.17
	0.06(10)	0.08(10)	0.06(10)	0.08(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

a Groups with identical values may vary in statistical significance, because tabulated statistics are rounded to fewer decimal places than the values used for statistical determination.

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 10

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
AST (U/L)				
DAY 29	109	112	145@	157@
	14(10)	8(10)	41(10)	79(10)
ALT (U/L)				
DAY 29	50	60	100@	111@
	8(10)	15(10)	37(10)	66(10)
SDH (U/L)				
DAY 29	12.8	13.5	20.6	13.9
	2.9(10)	3.8(10)	10.5(10)	5.0(10)
ALKP (U/L)				
DAY 29	201	214	225	274*
	37(10)	37(10)	46(10)	52(10)
BILI (mg/dL)				
DAY 29	0.09	0.12	0.12	0.12@
	0.03(10)	0.02(10)	0.01(10)	0.04(10)
BUN (mg/dL)				
DAY 29	15	15	15	15
	2(10)	2(10)	2(10)	2(10)
CREA (mg/dL)				
DAY 29	0.38	0.39	0.42	0.41
	0.04(10)	0.03(10)	0.05(10)	0.04(10)
CHOL (mg/dL)				
DAY 29	43	51*	51*	57*
	6(10)	5(10)	7(10)	6(10)
TRIG (mg/dL)				
DAY 29	30	44	45	56@
	10(10)	15(10)	15(10)	19(10)
GLUC (mg/dL)				
DAY 29	91	97	97	101
	8(10)	13(10)	9(10)	10(10)
TP (g/dL)				
DAY 29	6.7	6.7	6.5	6.7
	0.2(10)	0.3(10)	0.2(10)	0.2(10)
ALB (g/dL)				
DAY 29	4.3	4.2	4.1*	4.1
	0.2(10)	0.1(10)	0.2(10)	0.1(10)

TABLE 10 (Continued)

SUMMARY OF CLINICAL CHEMISTRY VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
GLOB (g/dL)				
DAY 29	2.4	2.5	2.4	2.5
	0.2(10)	0.3(10)	0.1(10)	0.1(10)
CALC (mg/dL)				
DAY 29	10.8	10.8	10.5	10.5
	0.4(10)	0.4(10)	0.3(10)	0.2(10)
IPHS (mg/dL)				
DAY 29	8.1	8.0	7.9	8.0
	0.5(10)	0.5(10)	0.5(10)	0.4(10)
NA (mmol/L)				
DAY 29	150.0	149.8	149.7	149.0
	1.5(10)	1.6(10)	1.2(10)	1.4(10)
K (mmol/L)				
DAY 29	6.19	6.05	6.22	5.99
	0.22(10)	0.40(10)	0.39(10)	0.32(10)
CL (mmol/L)				
DAY 29	102.4	102.5	103.9	102.5
	1.6(10)	1.9(10)	1.5(10)	1.4(10)
PFLU (µg/mL)				
DAY 29	0.1	0.1	0.1	0.1
	0.0(10)	0.0(10)	0.0(10)	0.0(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 11

SUMMARY OF URINALYSIS VALUES FOR MALE RATS

	Group I 0 mg/kg	Group III 10 mg/kg	Group V 100 mg/kg	Group VII 1000 mg/kg
VOL (mL)				
DAY 29	8.6	10.2	7.7	10.8
	7.6(10)	6.3(10)	3.9(10)	3.3(10)
UOSM (mOsm)				
DAY 29	1551	1235	1283	962@
	903(10)	511(10)	328(10)	284(10)
pH				
DAY 29	6.8	6.9	7.2	6.8
	0.3(10)	0.6(10)	0.7(9)	0.5(10)
URO (EU/dL)				
DAY 29	0.3	0.2	0.2	0.2
	0.3(10)	0.0(10)	0.0(9)	0.0(10)
UFLU (µg)				
DAY 29	14.8	17.4	19.2	33.9@
	4.0(9)	4.3(10)	5.3(10)	12.1(10)
UMTP (mg/dL)				
DAY 29	111	60	61	34*
	67(10)	28(10)	38(10)	11(10)

Data arranged as: Mean
Standard deviation (Number of values included in calculation)

* Statistically significant difference from control at $p < 0.05$ by Dunnett/Tamhane-Dunnett test.
@ Statistically significant difference from control at $p < 0.05$ by Dunn's test.

TABLE 12

MEAN FINAL BODY AND ORGAN WEIGHTS FROM MALE RATS

	MEAN FINAL BODY AND ABSOLUTE ORGAN WEIGHTS (GRAMS)			
Group:	I	III	V	VII
Dosage (mg/kg)	0	10	100	1000
LIVER	10.794	11.105	10.252	11.574
	1.266 (10)	1.372 (10)	1.004 (10)	1.223 (10)
KIDNEYS	3.014	3.137	2.915	3.105
	0.413 (10)	0.330 (10)	0.302 (10)	0.316 (10)
THYROID GLAND	0.017	0.020	0.017	0.018
	0.003 (9)	0.004 (10)	0.002 (10)	0.002 (10)
FINAL BODY WEIGHT	347.622	367.770	342.030	357.880
	24.048 (9)	33.563 (10)	20.450 (10)	24.679 (10)
	MEAN RELATIVE ORGAN WEIGHTS (% OF BODY WEIGHT)			
LIVER/ FINAL BODY * 100	3.081	3.016	2.992	3.234
	0.277 (9)	0.192 (10)	0.158 (10)	0.254 (10)
KIDNEYS/ FINAL BODY * 100	0.865	0.853	0.851	0.869
	0.078 (9)	0.043 (10)	0.062 (10)	0.078 (10)
THYROID GLAND/ FINAL BODY * 100	0.005	0.005	0.005	0.005
	0.001 (8)	0.001 (10)	0.001 (10)	0.001 (10)

Data summarized as: Mean
Standard Deviation (n); n < 10 reflects weighing error.
There were no statistically significant differences at $p < 0.05$ by Jonckheere-Terpstra trend test.

TABLE 13

INCIDENCES OF GROSS OBSERVATIONS IN MALE RATS

LESIONS	TREATMENT	LESION INCIDENCE (Numeric) 0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
LIVER		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
KIDNEYS		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	9	10
DILATATION, UNILATERAL.				1	
THYROID GLAND		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
SKIN		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10
TESTES				(1)	
LARGE, BILATERAL.				1	
TEETH		(10)	(10)	(10)	(10)
NO ABNORMALITY DETECTED		10	10	10	10

Figures in parentheses is the number of animals grossly examined for this tissue
The absence of a number indicates the finding specified was not identified

TABLE 14

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC) 0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
DIGESTIVE SYSTEM					
LIVER		(10)			(10)
NECROSIS, HEPATOCELLULAR, FOCAL.					
minimal					1
total observations per lesion					1
MACROPHAGES, PIGMENTED, FOCAL.					
minimal		1			
total observations per lesion		1			
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL.					
minimal		5			8
total observations per lesion		5			8
HEMATOPOIESIS, EXTRAMEDULLARY.					
minimal		10			10
total observations per lesion		10			10

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 14 (CONTINUED)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC) 0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
URINARY SYSTEM					
KIDNEYS		(10)		(1)	(10)
NO ABNORMALITY DETECTED		5			4
NEPHROPATHY, CHRONIC PROGRESSIVE.					
minimal		5			6
total observations per lesion		5			6
DILATATION, PELVIS, UNILATERAL.					
mild				1	
total observations per lesion				1	
ENDOCRINE SYSTEM					
THYROID GLAND		(10)			(10)
NO ABNORMALITY DETECTED		10			10
REPRODUCTIVE SYSTEM					
TESTES				(1)	
NO ABNORMALITY DETECTED				1	
NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.				1	

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

TABLE 14 (CONTINUED)

INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

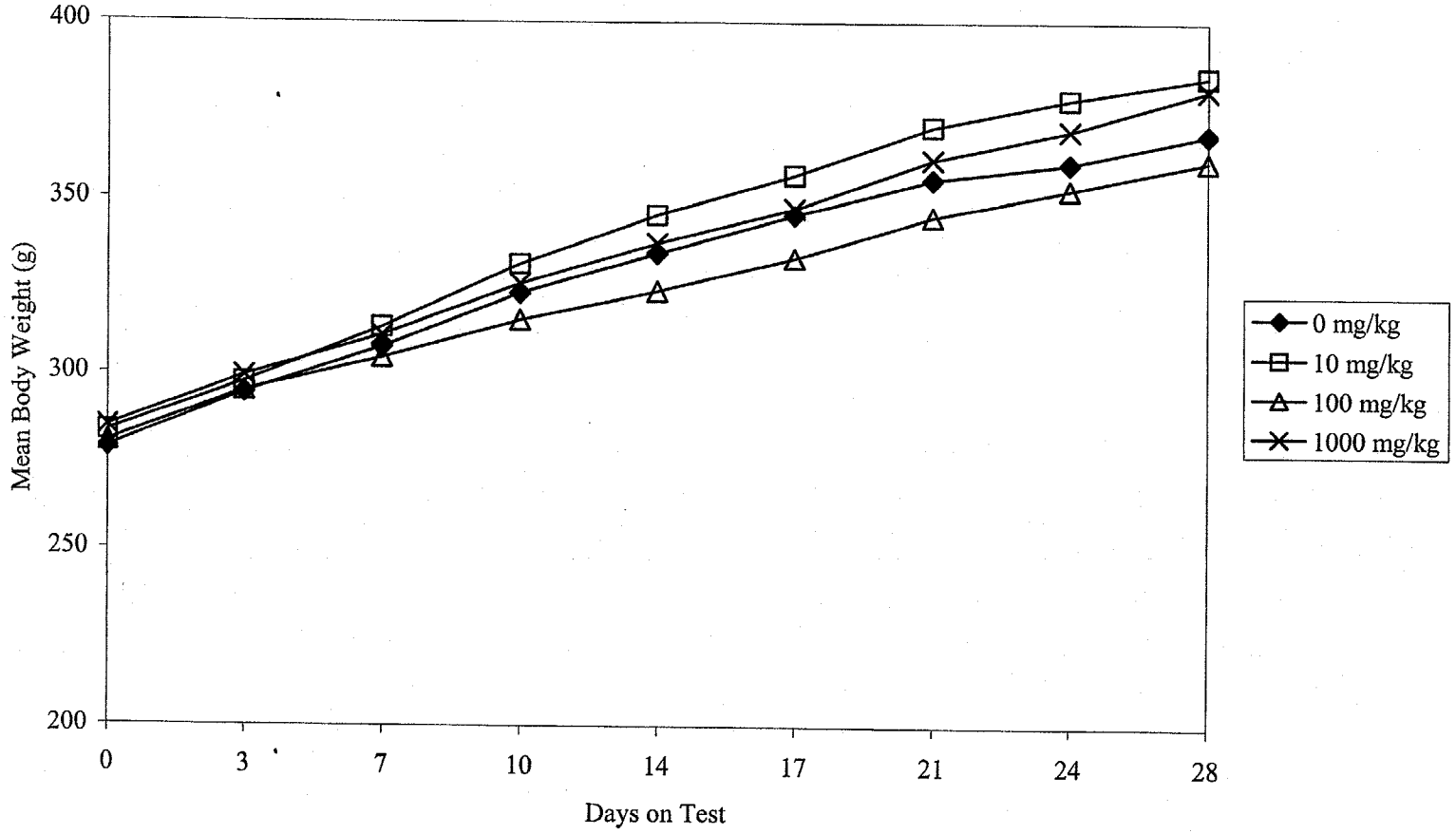
LESIONS	TREATMENT	LESION INCIDENCE (NUMERIC) 0 mg/kg I	10 mg/kg III	100 mg/kg V	1000 mg/kg VII
CUTANEOUS SYSTEM					
SKIN		(10)			(10)
NO ABNORMALITY DETECTED		10			10
TISSUES NOT INCLUDED WITHIN BODY SYSTEMS					
TEETH		(10)			(10)
NO ABNORMALITY DETECTED		10			9
INFLAMMATION, ACUTE.					
mild					1
total observations per lesion					1
HEMORRHAGE.					
mild					1
total observations per lesion					1

Figure in parentheses is number of animals microscopically examined for this tissue
The absence of a number indicates the lesion specified was not identified

FIGURES

FIGURE 1

MEAN BODY WEIGHTS OF MALE RATS



APPENDICES

APPENDIX A

Individual Daily Applied Dose Volumes

Individual Daily Applied Dose Volumes

	dermal µl Day 0	dermal µl Day 1	dermal µl Day 2	dermal µl Day 3	dermal µl Day 4	dermal µl Day 5	dermal µl Day 6	dermal µl Day 7	dermal µl Day 8
Male, I 0 mg/kg									
665732	248.0	248.0	248.0	264.8	264.8	264.8	264.8	278.2	278.2
665733	253.0	253.0	253.0	270.1	270.1	270.1	270.1	290.0	290.0
665734	261.7	261.7	261.7	271.9	271.9	271.9	271.9	279.7	279.7
665735	239.7	239.7	239.7	240.8	240.8	240.8	240.8	244.4	244.4
665736	237.6	237.6	237.6	259.2	259.2	259.2	259.2	270.6	270.6
665737	237.7	237.7	237.7	250.7	250.7	250.7	250.7	260.4	260.4
665738	207.7	207.7	207.7	215.4	215.4	215.4	215.4	225.7	225.7
665739	260.8	260.8	260.8	280.1	280.1	280.1	280.1	296.7	296.7
665740	251.2	251.2	251.2	270.3	270.3	270.3	270.3	281.2	281.2
665741	225.0	225.0	225.0	237.7	237.7	237.7	237.7	248.4	248.4
Male, III 10 mg/kg									
665742	2.2	2.2	2.2	2.4	2.4	2.4	2.4	2.5	2.5
665743	2.3	2.3	2.3	2.4	2.4	2.4	2.4	2.5	2.5
665744	2.5	2.5	2.5	2.7	2.7	2.7	2.7	2.8	2.8
665745	2.5	2.5	2.5	2.6	2.6	2.6	2.6	2.7	2.7
665746	2.4	2.4	2.4	2.6	2.6	2.6	2.6	2.7	2.7
665747	2.5	2.5	2.5	2.6	2.6	2.6	2.6	2.8	2.8
665748	2.4	2.4	2.4	2.5	2.5	2.5	2.5	2.6	2.6
665749	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.7	2.7
665750	2.6	2.6	2.6	2.8	2.8	2.8	2.8	2.9	2.9
665751	2.7	2.7	2.7	2.9	2.9	2.9	2.9	3.0	3.0
Male, V 100 mg/kg									
665752	24.2	24.2	24.2	25.9	25.9	25.9	25.9	27.2	27.2
665753	24.1	24.1	24.1	26.2	26.2	26.2	26.2	26.4	26.4
665754	25.3	25.3	25.3	27.2	27.2	27.2	27.2	28.0	28.0
665755	24.1	24.1	24.1	25.3	25.3	25.3	25.3	25.8	25.8
665756	24.8	24.8	24.8	25.6	25.6	25.6	25.6	26.1	26.1
665757	23.6	23.6	23.6	24.7	24.7	24.7	24.7	25.4	25.4
665758	24.0	24.0	24.0	24.4	24.4	24.4	24.4	26.1	26.1
665759	25.2	25.2	25.2	26.4	26.4	26.4	26.4	27.7	27.7
665760	26.0	26.0	26.0	26.7	26.7	26.7	26.7	27.2	27.2
665761	22.6	22.6	22.6	24.4	24.4	24.4	24.4	24.9	24.9

Individual Daily Applied Dose Volumes

	dermal µl Day 0	dermal µl Day 1	dermal µl Day 2	dermal µl Day 3	dermal µl Day 4	dermal µl Day 5	dermal µl Day 6	dermal µl Day 7	dermal µl Day 8
Male, VII 1000 mg/kg									
665762	241.7	241.7	241.7	251.1	251.1	251.1	251.1	258.8	258.8
665763	245.0	245.0	245.0	265.2	265.2	265.2	265.2	273.7	273.7
665764	262.3	262.3	262.3	263.1	263.1	263.1	263.1	275.4	275.4
665765	241.7	241.7	241.7	254.3	254.3	254.3	254.3	271.0	271.0
665766	238.2	238.2	238.2	261.6	261.6	261.6	261.6	277.0	277.0
665767	236.6	236.6	236.6	246.7	246.7	246.7	246.7	255.6	255.6
665768	251.8	251.8	251.8	264.6	264.6	264.6	264.6	275.5	275.5
665769	261.4	261.4	261.4	273.7	273.7	273.7	273.7	284.8	284.8
665770	260.8	260.8	260.8	284.3	284.3	284.3	284.3	289.8	289.8
665771	236.3	236.3	236.3	238.7	238.7	238.7	238.7	243.3	243.3

Individual Daily Applied Dose Volumes

	dermal µl Day 9	dermal µl Day 10	dermal µl Day 11	dermal µl Day 12	dermal µl Day 13	dermal µl Day 14	dermal µl Day 15	dermal µl Day 16	dermal µl Day 17
Male, I 0 mg/kg									
665732	278.2	293.8	293.8	293.8	293.8	306.9	306.9	306.9	309.7
665733	290.0	302.4	302.4	302.4	302.4	313.0	313.0	313.0	328.3
665734	279.7	290.3	290.3	290.3	290.3	293.7	293.7	293.7	302.9
665735	244.4	254.0	254.0	254.0	254.0	260.0	260.0	260.0	268.5
665736	270.6	287.0	287.0	287.0	287.0	291.7	291.7	291.7	308.0
665737	260.4	270.0	270.0	270.0	270.0	290.3	290.3	290.3	295.9
665738	225.7	234.7	234.7	234.7	234.7	248.3	248.3	248.3	260.0
665739	296.7	310.6	310.6	310.6	310.6	321.7	321.7	321.7	332.0
665740	281.2	298.1	298.1	298.1	298.1	307.5	307.5	307.5	321.8
665741	248.4	267.7	267.7	267.7	267.7	274.5	274.5	274.5	278.0
Male, III 10 mg/kg									
665742	2.5	2.7	2.7	2.7	2.7	2.9	2.9	2.9	2.9
665743	2.5	2.6	2.6	2.6	2.6	2.7	2.7	2.7	2.8
665744	2.8	2.9	2.9	2.9	2.9	3.0	3.0	3.0	3.1
665745	2.7	2.9	2.9	2.9	2.9	3.1	3.1	3.1	3.2
665746	2.7	2.9	2.9	2.9	2.9	3.0	3.0	3.0	3.1
665747	2.8	3.0	3.0	3.0	3.0	3.1	3.1	3.1	3.2
665748	2.6	2.7	2.7	2.7	2.7	2.8	2.8	2.8	2.8
665749	2.7	2.8	2.8	2.8	2.8	2.9	2.9	2.9	3.1
665750	2.9	3.1	3.1	3.1	3.1	3.3	3.3	3.3	3.4
665751	3.0	3.2	3.2	3.2	3.2	3.3	3.3	3.3	3.4
Male, V 100 mg/kg									
665752	27.2	28.8	28.8	28.8	28.8	29.6	29.6	29.6	29.7
665753	26.4	27.3	27.3	27.3	27.3	28.2	28.2	28.2	28.6
665754	28.0	29.0	29.0	29.0	29.0	29.8	29.8	29.8	31.9
665755	25.8	26.5	26.5	26.5	26.5	27.3	27.3	27.3	28.5
665756	26.1	27.4	27.4	27.4	27.4	28.7	28.7	28.7	29.4
665757	25.4	26.1	26.1	26.1	26.1	26.7	26.7	26.7	27.7
665758	26.1	27.9	27.9	27.9	27.9	28.8	28.8	28.8	29.1
665759	27.7	27.7	27.7	27.7	27.7	27.7	27.7	27.7	28.2
665760	27.2	28.0	28.0	28.0	28.0	29.0	29.0	29.0	30.0
665761	24.9	25.3	25.3	25.3	25.3	25.5	25.5	25.5	26.6

Individual Daily Applied Dose Volumes

	dermal µl Day 9	dermal µl Day 10	dermal µl Day 11	dermal µl Day 12	dermal µl Day 13	dermal µl Day 14	dermal µl Day 15	dermal µl Day 16	dermal µl Day 17
Male, VII 1000 mg/kg									
665762	258.8	268.4	268.4	268.4	268.4	275.0	275.0	275.0	269.8
665763	273.7	280.4	280.4	280.4	280.4	297.9	297.9	297.9	310.8
665764	275.4	291.7	291.7	291.7	291.7	296.4	296.4	296.4	306.3
665765	271.0	283.8	283.8	283.8	283.8	299.3	299.3	299.3	306.7
665766	277.0	291.1	291.1	291.1	291.1	300.9	300.9	300.9	323.2
665767	255.6	263.4	263.4	263.4	263.4	273.4	273.4	273.4	278.3
665768	275.5	289.4	289.4	289.4	289.4	310.5	310.5	310.5	315.5
665769	284.8	294.4	294.4	294.4	294.4	296.4	296.4	296.4	317.7
665770	289.8	307.5	307.5	307.5	307.5	313.3	313.3	313.3	313.1
665771	243.3	261.6	261.6	261.6	261.6	270.8	270.8	270.8	279.7

Individual Daily Applied Dose Volumes

	dermal µl Day 18	dermal µl Day 19	dermal µl Day 20	dermal µl Day 21	dermal µl Day 22	dermal µl Day 23	dermal µl Day 24	dermal µl Day 25	dermal µl Day 26
Male, I 0 mg/kg									
665732	309.7	309.7	309.7	328.0	328.0	328.0	342.4	342.4	342.4
665733	328.3	328.3	328.3	331.9	331.9	331.9	341.7	341.7	341.7
665734	302.9	302.9	302.9	310.9	310.9	310.9	316.4	316.4	316.4
665735	268.5	268.5	268.5	286.8	286.8	286.8	290.3	290.3	290.3
665736	308.0	308.0	308.0	318.3	318.3	318.3	322.3	322.3	322.3
665737	295.9	295.9	295.9	295.1	295.1	295.1	294.6	294.6	294.6
665738	260.0	260.0	260.0	269.0	269.0	269.0	265.5	265.5	265.5
665739	332.0	332.0	332.0	338.5	338.5	338.5	335.4	335.4	335.4
665740	321.8	321.8	321.8	325.0	325.0	325.0	332.1	332.1	332.1
665741	278.0	278.0	278.0	288.9	288.9	288.9	290.4	290.4	290.4
Male, III 10 mg/kg									
665742	2.9	2.9	2.9	3.1	3.1	3.1	3.2	3.2	3.2
665743	2.8	2.8	2.8	2.8	2.8	2.8	2.9	2.9	2.9
665744	3.1	3.1	3.1	3.3	3.3	3.3	3.3	3.3	3.3
665745	3.2	3.2	3.2	3.3	3.3	3.3	3.5	3.5	3.5
665746	3.1	3.1	3.1	3.2	3.2	3.2	3.3	3.3	3.3
665747	3.2	3.2	3.2	3.4	3.4	3.4	3.4	3.4	3.4
665748	2.8	2.8	2.8	2.9	2.9	2.9	3.0	3.0	3.0
665749	3.1	3.1	3.1	3.2	3.2	3.2	3.2	3.2	3.2
665750	3.4	3.4	3.4	3.6	3.6	3.6	3.6	3.6	3.6
665751	3.4	3.4	3.4	3.5	3.5	3.5	3.6	3.6	3.6
Male, V 100 mg/kg									
665752	29.7	29.7	29.7	30.9	30.9	30.9	31.5	31.5	31.5
665753	28.6	28.6	28.6	28.8	28.8	28.8	30.4	30.4	30.4
665754	31.9	31.9	31.9	32.4	32.4	32.4	33.7	33.7	33.7
665755	28.5	28.5	28.5	30.6	30.6	30.6	31.6	31.6	31.6
665756	29.4	29.4	29.4	30.2	30.2	30.2	30.4	30.4	30.4
665757	27.7	27.7	27.7	29.1	29.1	29.1	28.7	28.7	28.7
665758	29.1	29.1	29.1	30.1	30.1	30.1	30.7	30.7	30.7
665759	28.2	28.2	28.2	30.0	30.0	30.0	31.1	31.1	31.1
665760	30.0	30.0	30.0	30.9	30.9	30.9	30.7	30.7	30.7
665761	26.6	26.6	26.6	27.1	27.1	27.1	27.9	27.9	27.9

Individual Daily Applied Dose Volumes

	dermal µl Day 18	dermal µl Day 19	dermal µl Day 20	dermal µl Day 21	dermal µl Day 22	dermal µl Day 23	dermal µl Day 24	dermal µl Day 25	dermal µl Day 26
Male, VII 1000 mg/kg									
665762	269.8	269.8	269.8	284.5	284.5	284.5	295.4	295.4	295.4
665763	310.8	310.8	310.8	318.3	318.3	318.3	336.6	336.6	336.6
665764	306.3	306.3	306.3	318.3	318.3	318.3	320.4	320.4	320.4
665765	306.7	306.7	306.7	317.9	317.9	317.9	329.1	329.1	329.1
665766	323.2	323.2	323.2	348.7	348.7	348.7	353.7	353.7	353.7
665767	278.3	278.3	278.3	292.4	292.4	292.4	300.1	300.1	300.1
665768	315.5	315.5	315.5	324.9	324.9	324.9	330.4	330.4	330.4
665769	317.7	317.7	317.7	323.1	323.1	323.1	321.7	321.7	321.7
665770	313.1	313.1	313.1	326.3	326.3	326.3	340.1	340.1	340.1
665771	279.7	279.7	279.7	286.4	286.4	286.4	285.7	285.7	285.7

Individual Daily Applied Dose Volumes

	dermal µl Day 27	dermal µl Day 28
Male, I 0 mg/kg		
665732	342.4	337.7
665733	341.7	348.0
665734	316.4	329.8
665735	290.3	304.8
665736	322.3	324.3
665737	294.6	298.2
665738	265.5	275.0
665739	335.4	349.8
665740	332.1	343.7
665741	290.4	292.3
Male, III 10 mg/kg		
665742	3.2	3.3
665743	2.9	2.9
665744	3.3	3.2
665745	3.5	3.6
665746	3.3	3.3
665747	3.4	3.6
665748	3.0	3.0
665749	3.2	3.2
665750	3.6	3.5
665751	3.6	3.7
Male, V 100 mg/kg		
665752	31.5	32.5
665753	30.4	30.9
665754	33.7	34.4
665755	31.6	31.7
665756	30.4	31.1
665757	28.7	30.5
665758	30.7	33.0
665759	31.1	31.1
665760	30.7	30.8
665761	27.9	27.7

Individual Daily Applied Dose Volumes

	dermal µl Day 27	dermal µl Day 28
Male, VII 1000 mg/kg		
665762	295.4	303.5
665763	336.6	339.2
665764	320.4	334.1
665765	329.1	337.5
665766	353.7	356.0
665767	300.1	305.9
665768	330.4	351.0
665769	321.7	333.1
665770	340.1	352.4
665771	285.7	301.6

APPENDIX B

Individual Body Weights

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 3	Body Weight g Day 7	Body Weight g Day 10	Body Weight g Day 14	Body Weight g Day 17	Body Weight g Day 21	Body Weight g Day 24	Body Weight g Day 28
Male, I 0 mg/kg									
665732	285.2	304.5	319.9	337.9	352.9	356.2	377.2	393.8	388.4
665733	291.0	310.6	333.5	347.8	360.0	377.5	381.7	393.0	400.2
665734	300.9	312.7	321.7	333.9	337.8	348.3	357.5	363.9	379.3
665735	275.6	276.9	281.1	292.1	299.0	308.8	329.8	333.9	350.5
665736	273.2	298.1	311.2	330.1	335.4	354.2	366.1	370.7	372.9
665737	273.3	288.3	299.5	310.5	333.8	340.3	339.4	338.8	342.9
665738	238.9	247.7	259.5	269.9	285.6	299.0	309.3	305.3	316.2
665739	299.9	322.1	341.2	357.2	369.9	381.8	389.3	385.7	402.3
665740	288.9	310.8	323.4	342.8	353.6	370.1	373.8	381.9	395.3
665741	258.8	273.4	285.7	307.9	315.7	319.7	332.2	334.0	336.2
Male, III 10 mg/kg									
665742	257.6	275.1	283.8	310.8	330.9	337.8	356.7	368.7	377.2
665743	263.3	280.9	289.9	300.8	311.9	320.5	326.0	328.3	338.6
665744	291.6	307.4	320.8	328.7	346.0	357.8	374.6	382.0	373.3
665745	285.0	297.4	315.4	335.7	351.0	362.4	382.7	396.8	416.7
665746	277.4	295.4	314.4	333.0	347.3	360.7	365.0	374.9	380.1
665747	285.6	294.9	322.6	344.5	361.6	373.2	387.0	395.1	410.8
665748	277.3	284.1	298.5	310.9	316.3	320.4	331.1	339.8	345.3
665749	285.2	291.3	305.1	325.8	334.3	350.7	364.6	373.3	371.3
665750	304.2	319.8	335.3	358.0	378.3	391.9	412.9	408.8	404.0
665751	305.3	329.2	347.6	364.4	377.6	392.1	405.4	415.8	430.7
Male, V 100 mg/kg									
665752	278.4	298.4	312.6	331.7	340.7	341.7	355.3	362.6	373.2
665753	277.7	300.8	303.5	314.5	324.6	329.3	331.0	349.4	355.6
665754	290.5	312.7	322.2	333.0	343.0	366.7	372.7	387.6	396.1
665755	277.1	290.4	296.3	305.2	313.8	328.2	351.5	363.8	364.5
665756	285.2	294.2	300.4	315.4	330.5	338.1	347.0	349.8	357.6
665757	271.3	283.9	292.1	300.4	307.6	318.1	335.1	329.5	351.1
665758	275.7	280.1	300.7	320.7	331.1	334.3	346.5	352.9	379.2
665759	289.8	303.7	318.5	318.7	318.6	324.2	345.3	358.0	357.3
665760	298.6	306.5	313.3	322.5	333.0	344.5	354.8	352.7	353.8
665761	260.0	280.1	286.7	291.4	293.5	306.1	312.0	321.4	318.7

Individual Body Weights

	Body Weight g Day 0	Body Weight g Day 3	Body Weight g Day 7	Body Weight g Day 10	Body Weight g Day 14	Body Weight g Day 17	Body Weight g Day 21	Body Weight g Day 24	Body Weight g Day 28
Male, VII 1000 mg/kg									
665762	277.9	288.8	297.6	308.7	316.3	310.3	327.2	339.7	349.0
665763	281.7	305.0	314.7	322.5	342.6	357.4	366.1	387.1	390.1
665764	301.6	302.6	316.7	335.5	340.9	352.2	366.1	368.5	384.2
665765	277.9	292.4	311.7	326.4	344.2	352.7	365.6	378.5	388.1
665766	273.9	300.8	318.6	334.8	346.0	371.7	401.0	406.8	409.4
665767	272.1	283.7	293.9	302.9	314.4	320.1	336.3	345.1	351.8
665768	289.6	304.3	316.8	332.8	357.1	362.8	373.6	380.0	403.6
665769	300.6	314.8	327.5	338.6	340.9	365.4	371.6	370.0	383.1
665770	299.9	326.9	333.3	353.6	360.3	360.1	375.3	391.1	405.3
665771	271.7	274.5	279.8	300.8	311.4	321.6	329.4	328.5	346.8

APPENDIX C

Individual Food Consumption

Individual Food Consumption

	Food Cons. g/anm/day Day 7	Food Cons. g/anm/day Day 14	Food Cons. g/anm/day Day 21	Food Cons. g/anm/day Day 28
Male, I 0 mg/kg				
665732	27.1	27.8	28.3	28.2
665733	27.4	27.4	28.2	28.4
665734	26.1	25.6	25.4	26.7
665735	21.5	22.2	24.3	26.5
665736	28.5	27.6	27.1	27.4
665737	27.3	27.6	26.1	27.1
665738	25.2	26.4	25.9	26.2
665739	28.3	26.7	27.3	28.5
665740	28.1	27.4	26.7	27.2
665741	27.4	27.2	24.5	26.4
Male, III 10 mg/kg				
665742	27.8	27.8	27.1	28.4
665743	24.9	24.5	24.5	26.8
665744	26.8	25.8	27.0	27.1
665745	25.0	26.9	27.9	29.9
665746	26.0	27.9	27.1	27.8
665747	26.6	28.6	27.0	27.0
665748	25.7	25.1	24.9	25.2
665749	23.1	24.9	25.5	26.4
665750	27.6	29.8	29.8	28.2
665751	28.4	27.7	27.8	28.3
Male, V 100 mg/kg				
665752	26.9	26.6	27.1	28.7
665753	25.8	24.6	25.4	28.0
665754	27.1	27.4	27.7	28.0
665755	27.2	26.5	27.7	28.1
665756	23.3	24.0	25.5	27.3
665757	24.5	26.0	25.6	26.9
665758	22.9	24.7	25.7	28.3
665759	25.2	25.3	25.9	24.3
665760	26.0	26.2	25.7	26.3
665761	27.1	24.7	25.0	26.4
Male, VII 1000 mg/kg				
665762	25.7	26.7	26.8	27.8
665763	29.0	29.5	28.2	28.9
665764	24.4	25.5	26.1	25.7
665765	25.6	26.6	25.9	27.1
665766	28.2	28.3	31.0	28.7
665767	24.4	24.5	26.0	26.5
665768	27.0	28.5	26.9	27.5
665769	26.6	27.4	29.6	27.2
665770	28.2	28.4	26.5	28.8
665771	22.2	25.2	24.9	26.9

APPENDIX D

Individual Clinical Observations and Mortality Records

INDIVIDUAL CLINICAL OBSERVATIONS AND MORTALITY RECORDS

EXPLANATORY NOTES

Clinical observations reported in this appendix were recorded during body weight collection. Clinical observations recorded post-dosing are not included.

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	I	665732	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	I	665733	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	I	665734	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	I	665735	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	I	665736	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	I	665737	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	I	665738	General observation, No Abnormality Detected	0,3,7,10,14,17,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Wound, Superficial, Abdomen	21,24
			Sacrificed by design	29
M	I	665739	General observation, No Abnormality Detected	0,3,7,10,14,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Hair Loss, Neck, Right	21,24
			Wound, Superficial, Shoulder, Left	17
			Sacrificed by design	29
M	I	665740	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	I	665741	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	III	665742	General observation, No Abnormality Detected	0,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Discharge, Nose, Red	3
			Sacrificed by design	29
M	III	665743	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	III	665744	General observation, No Abnormality Detected	0,3,7,10,14
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Wound, Superficial, Dorsal Body, outside of test area	17
			Wound, Superficial, Dorsal Body, out of the test area	24,28,29
			Wound, Superficial, Shoulder, Bilateral	21,24,28,29
			Wound, Superficial, Shoulder, Right	17
			Sacrificed by design	29
M	III	665745	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	III	665746	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Hair Loss, Forepaw, Left	28,29
			Sacrificed by design	29
M	III	665747	General observation, No Abnormality Detected	0,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Discharge, Nose, Red	3
			Sacrificed by design	29
M	III	665748	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	III	665749	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	III	665750	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	III	665751	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	V	665752	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	V	665753	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	V	665754	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	V	665755	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	V	665756	General observation, No Abnormality Detected	0,3,7
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Hair Loss, Forepaw, Left	14,17,21,24,28,29
			Hair Loss, Shoulder, Bilateral	29
			Wound, Superficial, Dorsal Body, outside test area	28
			Wound, Superficial, Forepaw, Left	10
			Wound, Superficial, Shoulder, Bilateral	21,24,28
			Wound, Superficial, Shoulder, Left	14,17
			Sacrificed by design	29
M	V	665757	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	V	665758	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	V	665759	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	V	665760	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	V	665761	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	VII	665762	General observation, No Abnormality Detected	0,3
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Hair Loss, Forepaw, Bilateral	7,10,14,17,21,24,28,29
			Wound, Superficial, Forelimb, Right	7,10
			Wound, Superficial, Forepaw, Left	7,10
			Sacrificed by design	29
M	VII	665763	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	VII	665764	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	VII	665765	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Sacrificed by design	29
M	VII	665766	General observation, No Abnormality Detected	0,3,7,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Eye Observations, Bled via Orbital for Clin Path, Right	3,9,21
			Hair Loss, Forepaw, Bilateral	10,14,17,21,24
			Sacrificed by design	29

Individual Clinical Observations and Mortality Records

Sex	Group	Animal	Observation	Days
M	VII	665767	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Discharge, Eye right, Red	29
			Sacrificed by design	29
M	VII	665768	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	VII	665769	General observation, No Abnormality Detected	0,3,7,10,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Wound, Superficial, Dorsal Body, outside the test area	14,17,21,24,28
			Sacrificed by design	29
M	VII	665770	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29
M	VII	665771	General observation, No Abnormality Detected	0,3,7,10,14,17,21,24,28,29
			Eye Observations, Bled via Orbital for Clin Path, Left	29
			Sacrificed by design	29

APPENDIX E

Individual Clinical Observations - Post-Dosing

INDIVIDUAL CLINICAL OBSERVATIONS- POST-DOSING

EXPLANATORY NOTES

Clinical observations reported in this appendix were recorded daily after removal of the test substance. Clinical observations recorded during body weight collection are not included.

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	I	665732	General observation, No Abnormality Detected	5,10-13,14,16,17,19-20,21-23,24-27
			Discharge, Eye bilateral, Red	1-2,3-4,6,7-8,9,28
			Discharge, Eye right, Red	0,15,18
			Swollen Observations, Face	1
M	I	665733	General observation, No Abnormality Detected	0,2,4-5,7-8,11-13,14,16,18-20,21-23,24-27,28
			Discharge, Eye bilateral, Red	1,3,6,9,17
			Discharge, Eye right, Red	10,15
M	I	665734	General observation, No Abnormality Detected	0,4-5,7,14-15,22,24-27,28
			Discharge, Eye bilateral, Red	1-2,3,6,8,9,12-13,17-19,21,23
			Discharge, Nose, Red	3
			Discharge, Eye right, Red	10-11,16,20
			Swollen Observations, Face	1,23
M	I	665735	General observation, No Abnormality Detected	2,3-6,7,9,11-13,14-15,17-19,21,24-27,28
			Discharge, Eye bilateral, Red	0-1,10,16,22-23
			Discharge, Eye left, Red	8
			Discharge, Eye right, Red	20
M	I	665736	General observation, No Abnormality Detected	4,7-8,9,10,13,14-16,17-20,23,24-26,28
			Discharge, Eye bilateral, Red	0-2,3,5-6,11-12,21-22,27
M	I	665737	General observation, No Abnormality Detected	11,13,14-15,17-20,25-26,28
			Discharge, Eye bilateral, Red	0-2,3-6,7-9,12,16,21-22,24,27
			Discharge, Eye right, Red	10,23

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	I	665738	General observation, No Abnormality Detected	10-13,15,17
			Discharge, Eye bilateral, Red	3-4,6,7,9,14,16,18-20,21-23,24-27,28
			Discharge, Eye right, Red	0-2,5,8
			Wound, Superficial, Abdomen	21-23,24-26
M	I	665739	General observation, No Abnormality Detected	0,2,3,5-6,7,9,10-11,16,19
			Discharge, Eye bilateral, Red	4,8,12-13,14-15,18,20,27,28
			Hair Loss, Neck, Right	21-23,24-26
			Wound, Superficial, Shoulder, Left	17-18
			Swollen Observations, Face	1,4
M	I	665740	General observation, No Abnormality Detected	1-2,4-6,7,10-13,14-16,17-20,21,23,24-27,28
			Discharge, Eye bilateral, Red	8-9,22
			Swollen Observations, Face	0,3
M	I	665741	General observation, No Abnormality Detected	1-2,4,10,12-13,16,19,21-22,24,26,28
			Discharge, Eye bilateral, Red	0,3,5-6,7-9,11,15,17-18,20,23,25,27
			Discharge, Eye right, Red	14

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	III	665742	General observation, No Abnormality Detected	1-2,3-6,7-8,9,10-13,14-16,17-20,21,23,26-27,28
			Discharge, Eye bilateral, Red	22,24-25
			Discharge, Nose, Red	0
M	III	665743	General observation, No Abnormality Detected	1-2,6,7-8,9,10-13,14-16,17,19-20,21-23,24-27,28
			Discharge, Eye bilateral, Red	3-5,18
			Discharge, Nose, Red	3
			Discharge, Eye right, Red	0
M	III	665744	General observation, No Abnormality Detected	0,9,10-13,14-16
			Discharge, Eye bilateral, Red	2,3-4,7-8,19,23,24-25
			Discharge, Eye right, Red	1,5-6
			Wound, Superficial, Dorsal Body, out of the test area	21-23,24-27,28
			Wound, Superficial, Shoulder, Bilateral	20,21-23,24-27,28
			Wound, Superficial, Shoulder, Right	17-19
			Wound, Superficial, Neck	3
M	III	665745	General observation, No Abnormality Detected	1-2,5,7,10,13,15,19,27,28
			Discharge, Eye bilateral, Red	4,6,8,11-12,14,16,17-18,21-23
			Discharge, Eye right, Red	0,3,9,20,24-26
			Swollen Observations, Face	14
M	III	665746	General observation, No Abnormality Detected	1,5,7,9,10-13,14-16,17-20,22-23,24-26
			Discharge, Eye bilateral, Red	3-4,8,21
			Discharge, Eye right, Red	0,2,6
			Hair Loss, Forepaw, Left	27,28

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	III	665747	General observation, No Abnormality Detected	13,14-15,17,22-23,24-27
			Discharge, Eye bilateral, Red	0-2,3-6,7-9,10,16,18,20,28
			Discharge, Eye right, Red	11-12,19,21
M	III	665748	General observation, No Abnormality Detected	3-6,7,9,10,13,17,19-20,22,26-27
			Discharge, Eye bilateral, Red	0-2,8,11-12,14,16,18,21,23,24-25,28
			Discharge, Eye right, Red	15
M	III	665749	General observation, No Abnormality Detected	9,10,12-13,14-16,17,19-20,21-22,26-27,28
			Discharge, Eye bilateral, Red	0-2,3-6,7-8,11,23,24-25
			Discharge, Eye right, Red	18
M	III	665750	General observation, No Abnormality Detected	0-2,3-5,7,9,10-11,14,16,17,20,23,28
			Discharge, Eye bilateral, Red	6,8,12,15,18-19,21-22,24-27
			Discharge, Eye left, Red	13
M	III	665751	General observation, No Abnormality Detected	2,4-6,9,10-13,14,16,17-19,23,24-27,28
			Discharge, Eye bilateral, Red	3,7-8,15,21-22
			Discharge, Eye right, Red	0-1,20

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	V	665752	General observation, No Abnormality Detected	0,5-6,9,10-11,14,16,17,19-20,21-22,25
			Discharge, Eye bilateral, Red	3-4,8,12-13,15,18,23,24,26-27,28
			Discharge, Eye right, Red	1-2,7
M	V	665753	General observation, No Abnormality Detected	2,7,9,10-11,13,14-16,17,20,21,28
			Discharge, Eye bilateral, Red	1,3-6,8,12,18-19,22-23,24-27
			Discharge, Eye left, Red	0
M	V	665754	General observation, No Abnormality Detected	2,8,10-12,14,16,19,22,25-27
			Discharge, Eye bilateral, Red	1,3-6,7,9,13,15,18,20,23,24,28
			Discharge, Eye left, Red	21
			Discharge, Eye right, Red	17
			Swollen Observations, Face	0
M	V	665755	General observation, No Abnormality Detected	3,10
			Discharge, Eye bilateral, Red	0-2,6,7-8,9,11-13,14-16,17-20,21-23,24-27,28
			Discharge, Eye right, Red	4-5
M	V	665756	General observation, No Abnormality Detected	0,2,3,7
			Eye Observations, Dark, Right	4-6
			Discharge, Eye bilateral, Red	16,21-22,26
			Discharge, Eye left, Red	1
			Hair Loss, Forepaw, Left	13,14-16,17-20,21-23,24-27,28
			Wound, Superficial, Dorsal Body, outside test area	25-27,28
			Wound, Superficial, Forepaw, Left	8,9,10-12
			Wound, Superficial, Shoulder, Bilateral	20,21-23,24-27,28
			Wound, Superficial, Shoulder, Left	14-16

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	V	665757	General observation, No Abnormality Detected	1-2,3,7-8,10,13,14,20,23,24-26,28
			Discharge, Eye bilateral, Red	0,5-6,11-12,15-16,17,19,21-22,27
			Discharge, Eye right, Red	9,18
			Swollen Observations, Face	4
M	V	665758	General observation, No Abnormality Detected	2,8,11-12,14-16,17,19-20,22-23,27,28
			Discharge, Eye bilateral, Red	3-6,7,9,10,13,18,21,24-26
			Discharge, Eye right, Red	0-1
M	V	665759	General observation, No Abnormality Detected	0-2,4-6,7-9,10-13,14-16,17-18,20,21,24-27,28
			Discharge, Eye bilateral, Red	19,22-23
			Discharge, Nose, Red	3
M	V	665760	General observation, No Abnormality Detected	0-2,3-6,7-9,10-13,14-16,17-20,21,23,24-27,28
			Discharge, Eye bilateral, Red	22
M	V	665761	General observation, No Abnormality Detected	2,3-4,7-9,10-13,14-16,18-20,21-23,24-27,28
			Discharge, Eye bilateral, Red	0-1,5-6,17

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	VII	665762	General observation, No Abnormality Detected	1-2,3-6
			Discharge, Eye bilateral, Red	0,13,18,22
			Discharge, Eye right, Red	20
			Hair Loss, Forepaw, Bilateral	7-8,9,10-13,14-16,17-20,21-23,24-27,28
			Wound, Superficial, Forelimb, Right	7-8,9,10
			Wound, Superficial, Forepaw, Left	7-8,9,10
M	VII	665763	General observation, No Abnormality Detected	1,5-6,7-8,9,11,14-16,17-18,20,21-22,24-27,28
			Discharge, Eye bilateral, Red	0,3-4,12-13,19
			Discharge, Eye right, Red	2,10,23
M	VII	665764	General observation, No Abnormality Detected	9,10,14-15,17-20,21,23,24,27,28
			Discharge, Eye bilateral, Red	0-2,3-6,7-8,11-12,16,22,26
			Discharge, Eye left, Red	13
			Discharge, Eye right, Red	25
M	VII	665765	General observation, No Abnormality Detected	2,3-6,9,10-11,13,14,16,17-20,21-23,24-25,27,28
			Discharge, Eye bilateral, Red	0-1,7-8,12,15,26
M	VII	665766	General observation, No Abnormality Detected	7,9,24
			Discharge, Eye bilateral, Red	0-2,3-6,8,13,14,17-20,25-27,28
			Discharge, Nose, Red	6
			Discharge, Eye left, Red	12
			Discharge, Eye right, Red	11
			Hair Loss, Forepaw, Bilateral	10-13,14-16,17-20,21-23

Individual Clinical Observations - Post-Dosing

Sex	Group	Animal	Observation	Days
M	VII	665767	General observation, No Abnormality Detected	7,10-13,14-15,17-20,21-22,24-26
			Discharge, Eye bilateral, Red	0-2,3-6,8-9,16,23,27
			Discharge, Eye right, Red	28
M	VII	665768	General observation, No Abnormality Detected	0-2,3-5,7,10,14-15,17-18,20,21,23
			Discharge, Eye bilateral, Red	6,8-9,11-13,19,22,26-27,28
			Discharge, Eye right, Red	16,24-25
M	VII	665769	General observation, No Abnormality Detected	3-4,7-8,11
			Discharge, Eye bilateral, Red	0,5-6,9,12
			Discharge, Eye left, Red	1
			Discharge, Eye right, Red	10,13,14
			Wound, Superficial, Dorsal Body, outside the test area	14-16,17-20,21-23,24-27,28
			Wound, Superficial, Shoulder, Left	19
			Wound, Superficial, Neck	1-2
			Swollen Observations, Face	0-1
M	VII	665770	General observation, No Abnormality Detected	13,14-15,17,20,21-23,24,26-27,28
			Discharge, Eye bilateral, Red	0-2,5-6,7,9,11-12,18-19
			Discharge, Eye left, Red	25
			Discharge, Eye right, Red	3-4,8,10,16
			Swollen Observations, Face	0-1
M	VII	665771	General observation, No Abnormality Detected	0,3,8-9,12,14,16,17-20,21-23,24,26-27,28
			Discharge, Eye bilateral, Red	1-2,5-6,10-11,13,15,25
			Discharge, Eye left, Red	4
			Discharge, Eye right, Red	7

APPENDIX F

Individual Edema and Erythema Scores

INDIVIDUAL EDEMA AND ERYTHEMA SCORES

EXPLANATORY NOTES

DRAIZE[a] SCALE FOR SCORING SKIN IRRITATION

Evaluation of Skin Reactions	Score
Erythema and eschar formation:	
No erythema	0
Very slight erythema (barely perceptible)	1 (Slight)
Well-defined erythema	2 (Mild)
Moderate to severe erythema	3 (Moderate)
Severe erythema (beet redness) to slight eschar formation (injuries in depth)	4 (Severe)
Edema formation:	
No edema	0
Very slight edema (barely perceptible)	1 (Slight)
Slight edema (edges of area well defined by definite raising)	2 (Mild)
Moderate edema (raised approximately 1.0 mm)	3 (Moderate)
Severe edema (raised more than 1.0 mm extending beyond the area of exposure)	4 (Severe)

a Draize, J. H., "Dermal Toxicity." Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics. The Editorial Committee of the Association of Food and Drug Officials of the United States, Austin, Texas, 1959, pp. 46-59.

Individual Edema and Erythema Scores

	Edema Day 0	Edema Day 1	Edema Day 2	Edema Day 3	Edema Day 4	Edema Day 5	Edema Day 6	Edema Day 7	Edema Day 8	Edema Day 9	Edema Day 10	Edema Day 11
Male, I 0 mg/kg												
665732	0	0	0	0	0	0	0	0	0	0	0	0
665733	0	0	0	0	0	0	0	0	0	0	0	0
665734	0	0	0	0	0	0	0	0	0	0	0	0
665735	0	0	0	0	0	0	0	0	0	0	0	0
665736	0	0	0	0	0	0	0	0	0	0	0	0
665737	0	0	0	0	0	0	0	0	0	0	0	0
665738	0	0	0	0	0	0	0	0	0	0	0	0
665739	0	0	0	0	0	0	0	0	0	0	0	0
665740	0	0	0	0	0	0	0	0	0	0	0	0
665741	0	0	0	0	0	0	0	0	0	0	0	0
Male, III 10 mg/kg												
665742	0	0	0	0	0	0	0	0	0	0	0	0
665743	0	0	0	0	0	0	0	0	0	0	0	0
665744	0	0	0	0	0	0	0	0	0	0	0	0
665745	0	0	0	0	0	0	0	0	0	0	0	0
665746	0	0	0	0	0	0	0	0	0	0	0	0
665747	0	0	0	0	0	0	0	0	0	0	0	0
665748	0	0	0	0	0	0	0	0	0	0	0	0
665749	0	0	0	0	0	0	0	0	0	0	0	0
665750	0	0	0	0	0	0	0	0	0	0	0	0
665751	0	0	0	0	0	0	0	0	0	0	0	0
Male, V 100 mg/kg												
665752	0	0	0	0	0	0	0	0	0	0	0	0
665753	0	0	0	0	0	0	0	0	0	0	0	0
665754	0	0	0	0	0	0	0	0	0	0	0	0
665755	0	0	0	0	0	0	0	0	0	0	0	0
665756	0	0	0	0	0	0	0	0	0	0	0	0
665757	0	0	0	0	0	0	0	0	0	0	0	0
665758	0	0	0	0	0	0	0	0	0	0	0	0
665759	0	0	0	0	0	0	0	0	0	0	0	0
665760	0	0	0	0	0	0	0	0	0	0	0	0
665761	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Edema Day 0	Edema Day 1	Edema Day 2	Edema Day 3	Edema Day 4	Edema Day 5	Edema Day 6	Edema Day 7	Edema Day 8	Edema Day 9	Edema Day 10	Edema Day 11
Male, VII 1000 mg/kg												
665762	0	0	0	0	0	0	0	0	0	0	0	0
665763	0	0	0	0	0	0	0	0	0	0	0	0
665764	0	0	0	0	0	0	0	0	0	0	0	0
665765	0	0	0	0	0	0	0	0	0	0	0	0
665766	0	0	0	0	0	0	0	0	0	0	0	0
665767	0	0	0	0	0	0	0	0	0	0	0	0
665768	0	0	0	0	0	0	0	0	0	0	0	0
665769	0	0	0	0	0	0	0	0	0	0	0	0
665770	0	0	0	0	0	0	0	0	0	0	0	0
665771	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Edema Day 12	Edema Day 13	Edema Day 14	Edema Day 15	Edema Day 16	Edema Day 17	Edema Day 18	Edema Day 19	Edema Day 20	Edema Day 21	Edema Day 22	Edema Day 23
Male, I 0 mg/kg												
665732	0	0	0	0	0	0	0	0	0	0	0	0
665733	0	0	0	0	0	0	0	0	0	0	0	0
665734	0	0	0	0	0	0	0	0	0	0	0	0
665735	0	0	0	0	0	0	0	0	0	0	0	0
665736	0	0	0	0	0	0	0	0	0	0	0	0
665737	0	0	0	0	0	0	0	0	0	0	0	0
665738	0	0	0	0	0	0	0	0	0	0	0	0
665739	0	0	0	0	0	0	0	0	0	0	0	0
665740	0	0	0	0	0	0	0	0	0	0	0	0
665741	0	0	0	0	0	0	0	0	0	0	0	0
Male, III 10 mg/kg												
665742	0	0	0	0	0	0	0	0	0	0	0	0
665743	0	0	0	0	0	0	0	0	0	0	0	0
665744	0	0	0	0	0	0	0	0	0	0	0	0
665745	0	0	0	0	0	0	0	0	0	0	0	0
665746	0	0	0	0	0	0	0	0	0	0	0	0
665747	0	0	0	0	0	0	0	0	0	0	0	0
665748	0	0	0	0	0	0	0	0	0	0	0	0
665749	0	0	0	0	0	0	0	0	0	0	0	0
665750	0	0	0	0	0	0	0	0	0	0	0	0
665751	0	0	0	0	0	0	0	0	0	0	0	0
Male, V 100 mg/kg												
665752	0	0	0	0	0	0	0	0	0	0	0	0
665753	0	0	0	0	0	0	0	0	0	0	0	0
665754	0	0	0	0	0	0	0	0	0	0	0	0
665755	0	0	0	0	0	0	0	0	0	0	0	0
665756	0	0	0	0	0	0	0	0	0	0	0	0
665757	0	0	0	0	0	0	0	0	0	0	0	0
665758	0	0	0	0	0	0	0	0	0	0	0	0
665759	0	0	0	0	0	0	0	0	0	0	0	0
665760	0	0	0	0	0	0	0	0	0	0	0	0
665761	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Edema Day 12	Edema Day 13	Edema Day 14	Edema Day 15	Edema Day 16	Edema Day 17	Edema Day 18	Edema Day 19	Edema Day 20	Edema Day 21	Edema Day 22	Edema Day 23
Male, VII 1000 mg/kg												
665762	0	0	0	0	0	0	0	0	0	0	0	0
665763	0	0	0	0	0	0	0	0	0	0	0	0
665764	0	0	0	0	0	0	0	0	0	0	0	0
665765	0	0	0	0	0	0	0	0	0	0	0	0
665766	0	0	0	0	0	0	0	0	0	0	0	0
665767	0	0	0	0	0	0	0	0	0	0	0	0
665768	0	0	0	0	0	0	0	0	0	0	0	0
665769	0	0	0	0	0	0	0	0	0	0	0	0
665770	0	0	0	0	0	0	0	0	0	0	0	0
665771	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Edema Day 24	Edema Day 25	Edema Day 26	Edema Day 27	Edema Day 28
Male, I 0 mg/kg					
665732	0	0	0	0	0
665733	0	0	0	0	0
665734	0	0	0	0	0
665735	0	0	0	0	0
665736	0	0	0	0	0
665737	0	0	0	0	0
665738	0	0	0	0	0
665739	0	0	0	0	0
665740	0	0	0	0	0
665741	0	0	0	0	0
Male, III 10 mg/kg					
665742	0	0	0	0	0
665743	0	0	0	0	0
665744	0	0	0	0	0
665745	0	0	0	0	0
665746	0	0	0	0	0
665747	0	0	0	0	0
665748	0	0	0	0	0
665749	0	0	0	0	0
665750	0	0	0	0	0
665751	0	0	0	0	0
Male, V 100 mg/kg					
665752	0	0	0	0	0
665753	0	0	0	0	0
665754	0	0	0	0	0
665755	0	0	0	0	0
665756	0	0	0	0	0
665757	0	0	0	0	0
665758	0	0	0	0	0
665759	0	0	0	0	0
665760	0	0	0	0	0
665761	0	0	0	0	0

Individual Edema and Erythema Scores

	Edema Day 24	Edema Day 25	Edema Day 26	Edema Day 27	Edema Day 28
Male, VII 1000 mg/kg					
665762	0	0	0	0	0
665763	0	0	0	0	0
665764	0	0	0	0	0
665765	0	0	0	0	0
665766	0	0	0	0	0
665767	0	0	0	0	0
665768	0	0	0	0	0
665769	0	0	0	0	0
665770	0	0	0	0	0
665771	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 0	Erythema Day 1	Erythema Day 2	Erythema Day 3	Erythema Day 4	Erythema Day 5	Erythema Day 6	Erythema Day 7	Erythema Day 8	Erythema Day 9	Erythema Day 10	Erythema Day 11
Male, I 0 mg/kg												
665732	0	0	0	0	0	0	0	0	0	0	0	0
665733	0	0	0	0	0	0	0	0	0	0	0	0
665734	0	0	0	0	0	0	0	0	0	0	0	0
665735	0	0	0	0	0	0	0	0	0	0	0	0
665736	0	0	0	0	0	0	0	0	0	0	0	0
665737	0	0	0	0	0	0	0	0	0	0	0	0
665738	0	0	0	0	0	0	0	0	0	0	0	0
665739	0	0	0	0	0	0	0	0	0	0	0	0
665740	0	0	0	0	0	0	0	0	0	0	0	0
665741	0	0	0	0	0	0	0	0	0	0	0	0
Male, III 10 mg/kg												
665742	0	0	0	0	0	0	0	0	0	0	0	0
665743	0	0	0	0	0	0	0	0	0	0	0	0
665744	0	0	0	0	0	0	0	0	0	0	0	0
665745	0	0	0	0	0	0	0	0	0	0	0	0
665746	0	0	0	0	0	0	0	0	0	0	0	0
665747	0	0	0	0	0	0	0	0	0	0	0	0
665748	0	0	0	0	0	0	0	0	0	0	0	0
665749	0	0	0	0	0	0	0	0	0	0	0	0
665750	0	0	0	0	0	0	0	0	0	0	0	0
665751	0	0	0	0	0	0	0	0	0	0	0	0
Male, V 100 mg/kg												
665752	0	0	0	0	0	0	0	0	0	0	0	0
665753	0	0	0	0	0	0	0	0	0	0	0	0
665754	0	0	0	0	0	0	0	0	0	0	0	0
665755	0	0	0	0	0	0	0	0	0	0	0	0
665756	0	0	0	0	0	0	0	0	0	0	0	0
665757	0	0	0	0	0	0	0	0	0	0	0	0
665758	0	0	0	0	0	0	0	0	0	0	0	0
665759	0	0	0	0	0	0	0	0	0	0	0	0
665760	0	0	0	0	0	0	0	0	0	0	0	0
665761	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 0	Erythema Day 1	Erythema Day 2	Erythema Day 3	Erythema Day 4	Erythema Day 5	Erythema Day 6	Erythema Day 7	Erythema Day 8	Erythema Day 9	Erythema Day 10	Erythema Day 11
Male, VII 1000 mg/kg												
665762	0	0	0	0	0	0	0	0	0	0	0	0
665763	0	0	0	0	0	0	0	0	0	0	0	0
665764	0	0	0	0	0	0	0	0	0	0	0	0
665765	0	0	0	0	0	0	0	0	0	0	0	0
665766	0	0	0	0	0	0	0	0	0	0	0	0
665767	0	0	0	0	0	0	0	0	0	0	0	0
665768	0	0	0	0	0	0	0	0	0	0	0	0
665769	0	0	0	0	0	0	0	0	0	0	0	0
665770	0	0	0	0	0	0	0	0	0	0	0	0
665771	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 12	Erythema Day 13	Erythema Day 14	Erythema Day 15	Erythema Day 16	Erythema Day 17	Erythema Day 18	Erythema Day 19	Erythema Day 20	Erythema Day 21	Erythema Day 22	Erythema Day 23
Male, I 0 mg/kg												
665732	0	0	0	0	0	0	0	0	0	0	0	0
665733	0	0	0	0	0	0	0	0	0	0	0	0
665734	0	0	0	0	0	0	0	0	0	0	0	0
665735	0	0	0	0	0	0	0	0	0	0	0	0
665736	0	0	0	0	0	0	0	0	0	0	0	0
665737	0	0	0	0	0	0	0	0	0	0	0	0
665738	0	0	0	0	0	0	0	0	0	0	0	0
665739	0	0	0	0	0	0	0	0	0	0	0	0
665740	0	0	0	0	0	0	0	0	0	0	0	0
665741	0	0	0	0	0	0	0	0	0	0	0	0
Male, III 10 mg/kg												
665742	0	0	0	0	0	0	0	0	0	0	0	0
665743	0	0	0	0	0	0	0	0	0	0	0	0
665744	0	0	0	0	0	0	0	0	0	0	0	0
665745	0	0	0	0	0	0	1	0	0	0	0	0
665746	0	0	0	0	0	0	0	0	0	0	0	0
665747	0	0	0	0	0	0	0	0	0	0	0	0
665748	0	0	0	0	0	0	0	0	0	0	0	0
665749	0	0	0	0	0	0	0	0	0	0	0	0
665750	0	0	0	0	0	0	0	0	0	0	0	0
665751	0	0	0	0	0	0	0	0	0	0	0	0
Male, V 100 mg/kg												
665752	0	0	0	0	0	0	0	0	0	0	0	0
665753	0	0	0	0	0	0	0	0	0	0	0	0
665754	0	0	0	0	0	0	0	0	0	0	0	0
665755	0	0	0	0	1	0	0	0	0	0	0	0
665756	0	0	0	0	0	0	0	0	0	0	0	0
665757	0	0	0	0	0	0	0	0	0	0	0	0
665758	0	0	0	0	0	0	0	0	0	0	0	0
665759	0	0	0	0	0	0	0	0	0	0	0	0
665760	0	0	0	0	0	0	0	0	0	0	0	0
665761	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 12	Erythema Day 13	Erythema Day 14	Erythema Day 15	Erythema Day 16	Erythema Day 17	Erythema Day 18	Erythema Day 19	Erythema Day 20	Erythema Day 21	Erythema Day 22	Erythema Day 23
Male, VII 1000 mg/kg												
665762	0	0	0	0	0	0	0	0	0	0	0	0
665763	0	0	0	0	0	0	0	0	0	0	0	0
665764	0	0	0	0	0	0	0	0	0	0	0	0
665765	0	0	0	0	0	0	0	0	0	0	0	0
665766	0	0	0	0	0	0	0	0	0	0	0	0
665767	0	0	0	0	0	0	0	0	0	0	0	0
665768	0	0	0	0	0	0	0	0	0	0	0	0
665769	0	0	0	0	0	0	0	0	0	0	0	0
665770	0	0	0	0	0	0	0	0	0	0	0	0
665771	0	0	0	0	0	0	0	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 24	Erythema Day 25	Erythema Day 26	Erythema Day 27	Erythema Day 28
Male, I 0 mg/kg					
665732	0	0	0	0	0
665733	0	0	0	0	0
665734	0	0	0	0	0
665735	0	0	0	0	0
665736	0	0	0	0	0
665737	0	0	0	0	0
665738	0	0	0	0	0
665739	0	0	0	0	0
665740	0	0	0	0	0
665741	0	0	0	0	0
Male, III 10 mg/kg					
665742	0	0	0	0	0
665743	0	0	0	0	0
665744	0	0	0	0	0
665745	0	0	0	0	0
665746	0	0	0	0	0
665747	0	0	0	0	0
665748	0	0	0	0	0
665749	0	0	0	0	0
665750	0	0	0	0	0
665751	0	0	0	0	0
Male, V 100 mg/kg					
665752	0	0	0	0	0
665753	0	0	0	0	0
665754	0	0	0	0	0
665755	0	0	0	0	0
665756	0	0	0	0	0
665757	0	0	0	0	0
665758	0	0	0	0	0
665759	0	0	0	0	0
665760	0	0	0	0	0
665761	0	0	0	0	0

Individual Edema and Erythema Scores

	Erythema Day 24	Erythema Day 25	Erythema Day 26	Erythema Day 27	Erythema Day 28
Male, VII 1000 mg/kg					
665762	0	0	0	0	0
665763	0	0	0	0	0
665764	0	0	0	0	0
665765	0	0	0	0	0
665766	0	0	0	0	0
665767	0	0	0	1	0
665768	0	0	0	0	0
665769	0	0	0	0	0
665770	0	0	0	0	0
665771	0	0	0	0	0

APPENDIX G

Individual Blood Fluorine Levels

BLOOD FLUORINE LEVELS
TEST DAY 21

Animal Number	Group	Dosage (mg/kg/day)	Fluorine (ppm)
665732	I	0	<0.5[a]
665733	I	0	<0.5
665734	I	0	<0.5
665735	I	0	<0.5
665736	I	0	<0.5
665742	III	10	5.96
665743	III	10	<0.5
665744	III	10	0.97
665745	III	10	0.52
665746	III	10	<0.5
665752	V	100	0.78
665753	V	100	0.57
665754	V	100	0.54
665755	V	100	0.66
665756	V	100	0.6
665762	VII	1000	1.24
665763	VII	1000	<0.5
665764	VII	1000	<0.5
665765	VII	1000	1.22
665766	VII	1000	1.38

a <0.5 is below the limit of quantification

APPENDIX H

Individual Animal Clinical Pathology Data

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES

ABBREVIATIONS:

General:

ADEQ	-	adequate
NT	-	not taken or not performed
OK	-	sample condition OK for testing
QNS	-	quantity not sufficient for testing
RNV	-	result not valid
<	-	less than

Individual Hematology Values:

COND	-	sample condition
RBC	-	red blood cell count
HGB	-	hemoglobin
HCT	-	hematocrit
MCV	-	mean corpuscular volume
MCH	-	mean corpuscular hemoglobin
MCHC	-	mean corpuscular hemoglobin concentration
RDW	-	red cell distribution width
ARET	-	absolute reticulocyte count
PLT	-	platelet count
WBC	-	white blood cell count
ANEU	-	absolute neutrophil (all forms)
ALYM	-	absolute lymphocyte
AMON	-	absolute monocyte
AEOS	-	absolute eosinophil
ABAS	-	absolute basophil
ALUC	-	absolute large unstained cell

Individual Red Blood Cell Morphology Values:

NORM	-	Normal
ANIS	-	anisocytosis
MIC	-	microcytes
MAC	-	macrocytes
POLY	-	polychromasia
HYPO	-	hypochromasia
ECHI	-	echinocytes
ACAN	-	acanthocytes
TARG	-	Target cells
RX	-	rouleaux
HJB	-	Howell-Jolly body
-	-	not observed or not examined; see whole blood sample condition

Individual White Blood Cell / Platelet Morphology Values:

NORM	-	Normal
SM	-	Smudge white blood cells
TOX	-	toxic neutrophils
DB	-	Döhle bodies
VC	-	vacuolated cytoplasm
BC	-	basophilic cytoplasm
PCE	-	platelet clumps / estimate
GP	-	giant platelets
BP	-	bizarre platelets
-	-	not observed or not examined; see whole blood sample condition

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

ABBREVIATIONS: (Continued)

Individual Clinical Chemistry Values:

SHEM	-	serum hemolysis
SLIP	-	serum lipemia
SICT	-	serum icterus
AST	-	aspartate aminotransferase
ALT	-	alanine aminotransferase
SDH	-	sorbitol dehydrogenase
ALKP	-	alkaline phosphatase
BILI	-	total bilirubin
BUN	-	urea nitrogen
CREA	-	creatinine
CHOL	-	cholesterol
TRIG	-	triglycerides
GLUC	-	glucose
TP	-	total protein
ALB	-	albumin
GLOB	-	globulin
CALC	-	calcium
IPHS	-	inorganic phosphorous
NA	-	sodium
K	-	potassium
CL	-	chloride
PHEM	-	plasma hemolysis from blood sample for fluoride determination
PLIP	-	plasma lipemia from blood sample for fluoride determination
PICT	-	plasma icterus from blood sample for fluoride determination
PFLU	-	plasma fluoride

Individual Urinalysis Values:

QUAL	-	quality (modifies color)
COL	-	color
CLAR	-	clarity
VOL	-	volume
UOSM	-	urine osmolality
pH	-	the logarithm of the reciprocal of the hydrogen ion concentration
UGLU	-	urine glucose
KET	-	ketone
UBIL	-	urine bilirubin
BLD	-	blood
URO	-	urobilinogen
UFLU	-	urine fluoride
UMTP	-	urine protein

Individual Urine Microscopic Examination Values:

EPIT	-	epithelial cells
UWBC	-	urine white blood cells
URBC	-	urine red blood cells
NCRY	-	normal crystals
MICR	-	microorganisms
SPER	-	sperm

INDIVIDUAL ANIMAL CLINICAL PATHOLOGY DATA

EXPLANATORY NOTES (Continued)

NOTES:

When individual animal data are not reported, it may be due to one of the following reasons or other reasons, all of which are explained in the study records:

the sample was clotted (CLOT)
there was insufficient sample for testing (QNS)
a valid result could not be obtained (RNV)
the sample was not suitable for testing
the animal died prior to sample collection
no sample was available for testing (NSR)

When an individual observation was recorded as being less than a certain value, calculations were performed on half the recorded value. For example, if bilirubin was reported as <0.1, 0.05 was used for any calculations performed with that bilirubin data.

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$
Male, Group I - 0 mg/kg - Day 29											
665732	OK	8.15	16.2	47.7	58.5	19.9	34.0	11.4	209.3	1222	9.62
665733	OK	7.86	16.1	47.7	60.7	20.4	33.7	10.7	154.7	1344	8.99
665734	OK	8.00	15.4	46.0	57.5	19.3	33.5	10.9	221.5	1292	15.60
665735	OK	7.92	15.7	46.7	59.0	19.8	33.5	12.0	242.3	RNV	12.97
665736	OK	8.38	17.0	50.4	60.2	20.3	33.7	11.1	258.3	1039	11.79
665737	OK	8.88	16.8	49.7	56.0	19.0	33.8	10.7	143.9	1264	19.56
665738	OK	8.34	15.7	46.6	55.8	18.8	33.7	11.4	131.4	1141	9.73
665739	OK	8.63	17.2	51.3	59.4	19.9	33.6	10.1	149.2	991	10.46
665740	OK	8.35	16.1	47.0	56.3	19.3	34.2	10.8	130.3	1212	11.06
665741	OK	8.69	16.8	49.0	56.4	19.3	34.2	10.6	133.1	1172	10.68
Male, Group III - 10 mg/kg - Day 29											
665742	OK	7.79	15.4	45.7	58.6	19.8	33.8	11.7	208.6	1104	15.71
665743	OK	7.62	15.0	45.3	59.4	19.7	33.2	11.2	196.1	1338	10.20
665744	OK	8.07	16.4	46.9	58.2	20.4	35.0	10.7	209.1	1183	10.55
665745	OK	7.42	15.0	44.9	60.5	20.2	33.4	11.3	263.1	1284	10.11
665746	OK	7.97	16.2	48.0	60.2	20.3	33.7	10.9	181.2	RNV	8.37
665747	OK	7.93	16.0	46.3	58.4	20.2	34.7	11.7	215.2	RNV	14.84
665748	OK	8.45	16.3	47.5	56.2	19.3	34.3	11.0	144.4	1266	7.96
665749	OK	8.44	16.0	47.1	55.8	19.0	34.0	10.5	127.2	1445	15.66
665750	OK	8.26	16.5	48.1	58.3	19.9	34.2	11.2	141.4	1436	14.76
665751	OK	7.56	15.8	46.5	61.5	20.9	34.0	10.8	218.6	1162	13.55

Individual Hematology Values

Animal Number	COND	RBC $x10^6/\mu L$	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %	ARET $x10^3/\mu L$	PLT $x10^3/\mu L$	WBC $x10^3/\mu L$
Male, Group V - 100 mg/kg - Day 29											
665752	OK	8.19	16.0	48.2	58.8	19.6	33.3	11.2	183.5	1253	14.64
665753	OK	7.79	14.9	45.2	58.1	19.1	32.9	11.5	199.4	1369	11.19
665754	OK	7.66	15.1	43.5	56.8	19.7	34.6	11.0	253.9	1709	15.06
665755	OK	7.95	16.4	47.8	60.1	20.6	34.3	11.1	190.6	1306	15.60
665756	OK	7.42	15.1	44.2	59.6	20.3	34.1	11.0	240.4	1197	11.86
665757	OK	7.84	15.3	45.6	58.2	19.5	33.6	10.6	152.8	1181	12.56
665758	OK	7.57	15.2	43.7	57.8	20.0	34.7	11.0	145.5	1429	8.94
665759	OK	8.28	15.4	46.1	55.7	18.7	33.5	10.3	79.4	1191	14.99
665760	OK	8.49	16.5	48.2	56.8	19.4	34.2	10.7	175.8	1284	11.49
665761	OK	8.35	16.2	47.2	56.5	19.5	34.4	10.9	105.0	1342	12.19
Male, Group VII - 1000 mg/kg - Day 29											
665762	OK	7.97	15.6	46.5	58.3	19.6	33.7	10.7	191.0	942	12.13
665763	OK	8.37	16.2	47.2	56.5	19.3	34.2	10.5	189.4	1085	12.39
665764	OK	8.23	15.3	44.7	54.3	18.6	34.3	11.7	169.5	1355	10.35
665765	OK	7.80	15.6	46.2	59.2	20.0	33.7	11.6	262.3	1295	17.14
665766	OK	7.66	15.3	45.8	59.8	19.9	33.3	11.2	215.1	1426	16.53
665767	OK	8.23	15.3	45.4	55.2	18.6	33.7	11.8	180.0	1213	17.21
665768	OK	7.57	15.1	44.0	58.2	19.9	34.2	10.8	161.9	RNV	16.68
665769	OK	7.98	15.7	46.1	57.7	19.7	34.1	10.5	165.6	1436	13.65
665770	OK	8.08	15.9	45.9	56.8	19.7	34.7	11.0	128.1	RNV	15.88
665771	OK	8.24	15.7	45.7	55.4	19.0	34.4	11.3	188.1	1364	14.65

Individual Hematology Values

Animal Number	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Male, Group I - 0 mg/kg - Day 29						
665732	0.83	8.32	0.18	0.15	0.06	0.08
665733	1.00	7.42	0.27	0.13	0.06	0.11
665734	1.93	12.60	0.46	0.22	0.17	0.23
665735	1.65	10.35	0.45	0.19	0.16	0.17
665736	1.44	9.84	0.19	0.14	0.10	0.07
665737	4.02	14.48	0.44	0.19	0.18	0.24
665738	2.09	7.16	0.17	0.12	0.09	0.11
665739	0.98	8.66	0.22	0.34	0.09	0.17
665740	1.51	8.79	0.39	0.15	0.12	0.10
665741	1.51	8.52	0.31	0.08	0.15	0.10
Male, Group III - 10 mg/kg - Day 29						
665742	1.57	13.24	0.37	0.23	0.15	0.16
665743	1.82	7.61	0.30	0.25	0.07	0.13
665744	2.59	7.35	0.33	0.10	0.11	0.07
665745	0.88	8.59	0.21	0.27	0.08	0.09
665746	1.38	6.59	0.17	0.12	0.05	0.06
665747	2.19	11.76	0.21	0.43	0.12	0.14
665748	0.74	6.59	0.24	0.16	0.09	0.13
665749	1.26	13.43	0.28	0.19	0.14	0.34
665750	1.95	12.06	0.27	0.22	0.12	0.14
665751	1.55	11.24	0.29	0.17	0.12	0.18

Individual Hematology Values

Animal Number	ANEU $x10^3/\mu L$	ALYM $x10^3/\mu L$	AMON $x10^3/\mu L$	AEOS $x10^3/\mu L$	ABAS $x10^3/\mu L$	ALUC $x10^3/\mu L$
Male, Group V - 100 mg/kg - Day 29						
665752	1.24	12.54	0.33	0.18	0.12	0.23
665753	1.44	8.93	0.37	0.25	0.05	0.14
665754	1.36	12.93	0.39	0.16	0.07	0.15
665755	1.21	13.47	0.27	0.17	0.15	0.32
665756	1.89	9.27	0.29	0.22	0.08	0.11
665757	1.39	10.51	0.27	0.16	0.09	0.12
665758	1.46	6.92	0.30	0.09	0.03	0.14
665759	1.21	12.79	0.43	0.27	0.13	0.15
665760	1.13	9.63	0.24	0.28	0.09	0.13
665761	1.38	10.17	0.24	0.15	0.09	0.16
Male, Group VII - 1000 mg/kg - Day 29						
665762	1.41	9.73	0.35	0.23	0.30	0.10
665763	1.05	10.42	0.48	0.21	0.07	0.15
665764	1.13	8.52	0.32	0.20	0.12	0.06
665765	2.04	14.12	0.45	0.20	0.13	0.19
665766	2.95	12.44	0.51	0.25	0.12	0.26
665767	2.68	13.55	0.44	0.26	0.11	0.17
665768	2.91	12.33	0.68	0.29	0.14	0.32
665769	2.47	10.42	0.26	0.28	0.13	0.10
665770	1.69	13.12	0.42	0.33	0.11	0.21
665771	1.66	12.28	0.23	0.20	0.17	0.11

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Male, Group I - 0 mg/kg - Day 29											
665732	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
665733	NO	-	-	-	TRACE	-	MODERATE	TRACE	-	-	-
665734	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
665735	NO	-	-	-	TRACE	-	MANY	TRACE	-	-	-
665736	NO	-	-	-	TRACE	-	-	-	-	-	-
665737	NO	-	-	-	TRACE	-	FEW	-	-	-	-
665738	NO	-	-	-	TRACE	-	-	FEW	-	-	-
665739	NO	-	-	-	TRACE	-	-	-	-	-	-
665740	NO	-	-	-	TRACE	-	-	TRACE	-	-	-
665741	NO	-	-	-	TRACE	-	MANY	TRACE	-	-	-
Male, Group III - 10 mg/kg - Day 29											
665742	NO	-	-	-	TRACE	-	-	FEW	-	-	-
665743	NO	-	-	-	TRACE	-	-	FEW	-	-	-
665744	NO	-	-	-	TRACE	-	-	-	-	-	-
665745	NO	-	-	-	TRACE	-	MODERATE	TRACE	-	-	-
665746	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
665747	NO	-	-	-	TRACE	-	-	-	-	-	-
665748	NO	-	-	-	TRACE	-	FEW	-	-	-	-
665749	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
665750	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
665751	NO	-	-	-	TRACE	-	-	-	-	-	-

Individual Red Blood Cell Morphology Values

Animal Number	NORM	ANIS	MIC	MAC	POLY	HYPO	ECHI	ACAN	TARG	RX	HJB
Male, Group V - 100 mg/kg - Day 29											
665752	NO	-	-	-	TRACE	-	-	-	-	-	-
665753	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
665754	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
665755	NO	-	-	-	TRACE	-	FEW	-	-	-	-
665756	NO	-	-	-	TRACE	-	FEW	-	-	-	-
665757	NO	-	-	-	TRACE	-	FEW	FEW	-	-	-
665758	NO	-	-	-	TRACE	-	MODERATE	TRACE	-	-	-
665759	NO	-	-	-	TRACE	-	TRACE	-	-	-	-
665760	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
665761	NO	-	-	-	TRACE	-	-	-	-	-	-
Male, Group VII - 1000 mg/kg - Day 29											
665762	NO	-	-	-	TRACE	-	FEW	TRACE	-	-	-
665763	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
665764	NO	-	-	-	TRACE	-	MODERATE	MODERATE	-	-	-
665765	NO	-	-	-	TRACE	-	MODERATE	TRACE	-	-	-
665766	NO	-	-	-	TRACE	-	MODERATE	FEW	-	-	-
665767	NO	-	-	-	TRACE	-	MANY	MODERATE	-	-	-
665768	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
665769	NO	-	-	-	TRACE	-	-	-	-	-	-
665770	NO	-	-	-	TRACE	-	TRACE	TRACE	-	-	-
665771	NO	-	-	-	TRACE	-	TRACE	FEW	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Male, Group I - 0 mg/kg - Day 29									
665732	YES	-	-	-	-	-	-	-	-
665733	YES	-	-	-	-	-	-	-	-
665734	YES	-	-	-	-	-	-	-	-
665735	NO	-	-	-	-	-	YES/ADEQ	-	-
665736	YES	-	-	-	-	-	-	-	-
665737	YES	-	-	-	-	-	-	-	-
665738	YES	-	-	-	-	-	-	-	-
665739	YES	-	-	-	-	-	-	-	-
665740	YES	-	-	-	-	-	-	-	-
665741	YES	-	-	-	-	-	-	-	-
Male, Group III - 10 mg/kg - Day 29									
665742	YES	-	-	-	-	-	-	-	-
665743	YES	-	-	-	-	-	-	-	-
665744	YES	-	-	-	-	-	-	-	-
665745	YES	-	-	-	-	-	-	-	-
665746	NO	-	-	-	-	-	YES/ADEQ	-	-
665747	NO	-	-	-	-	-	YES/ADEQ	-	-
665748	YES	-	-	-	-	-	-	-	-
665749	YES	-	-	-	-	-	-	-	-
665750	YES	-	-	-	-	-	-	-	-
665751	YES	-	-	-	-	-	-	-	-

Individual White Blood Cell / Platelet Morphology Values

Animal Number	NORM	SM	TOX	DB	VC	BC	PCE	GP	BP
Male, Group V - 100 mg/kg - Day 29									
665752	YES	-	-	-	-	-	-	-	-
665753	YES	-	-	-	-	-	-	-	-
665754	YES	-	-	-	-	-	-	-	-
665755	YES	-	-	-	-	-	-	-	-
665756	YES	-	-	-	-	-	-	-	-
665757	YES	-	-	-	-	-	-	-	-
665758	YES	-	-	-	-	-	-	-	-
665759	YES	-	-	-	-	-	-	-	-
665760	YES	-	-	-	-	-	-	-	-
665761	YES	-	-	-	-	-	-	-	-
Male, Group VII - 1000 mg/kg - Day 29									
665762	YES	-	-	-	-	-	-	-	-
665763	YES	-	-	-	-	-	-	-	-
665764	YES	-	-	-	-	-	-	-	-
665765	NO	-	-	-	-	-	-	TRACE	-
665766	YES	-	-	-	-	-	-	-	-
665767	YES	-	-	-	-	-	-	-	-
665768	NO	-	-	-	-	-	YES/ADEQ	-	-
665769	YES	-	-	-	-	-	-	-	-
665770	NO	-	-	-	-	-	YES/ADEQ	-	-
665771	YES	-	-	-	-	-	-	-	-

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL
Male, Group I - 0 mg/kg - Day 29											
665732	TRACE	NONE	NONE	113	42	15.5	126	<0.10	16	0.34	39
665733	TRACE	NONE	NONE	106	49	14.0	187	0.12	14	0.40	36
665734	TRACE	NONE	NONE	117	52	11.8	197	<0.10	14	0.35	39
665735	NONE	NONE	NONE	112	59	12.2	176	0.10	13	0.39	49
665736	TRACE	NONE	NONE	130	63	14.2	232	0.11	16	0.46	51
665737	TRACE	NONE	NONE	95	55	7.2	213	0.10	13	0.35	42
665738	NONE	NONE	NONE	107	50	11.6	190	0.12	16	0.42	49
665739	TRACE	NONE	NONE	126	49	11.6	245	0.11	19	0.38	33
665740	NONE	NONE	NONE	89	35	11.7	197	<0.10	13	0.30	49
665741	NONE	NONE	NONE	94	50	18.0	251	0.11	17	0.38	43
Male, Group III - 10 mg/kg - Day 29											
665742	TRACE	NONE	NONE	117	73	12.8	176	0.11	12	0.40	53
665743	TRACE	NONE	NONE	118	65	14.0	205	0.10	14	0.37	58
665744	TRACE	NONE	NONE	110	50	15.4	187	0.16	19	0.39	47
665745	NONE	NONE	NONE	99	45	14.7	210	0.11	16	0.43	55
665746	NONE	NONE	NONE	119	57	16.8	237	0.12	18	0.40	45
665747	NONE	NONE	NONE	115	57	10.1	184	0.10	15	0.37	46
665748	NONE	NONE	NONE	99	42	13.6	171	0.12	17	0.44	50
665749	TRACE	NONE	NONE	124	91	12.5	234	0.11	14	0.39	58
665750	SMALL	NONE	NONE	108	51	5.6	288	0.12	13	0.33	53
665751	TRACE	NONE	NONE	109	65	19.8	244	0.12	13	0.37	48

Individual Clinical Chemistry Values

Animal Number	SHEM	SLIP	SICT	AST U/L	ALT U/L	SDH U/L	ALKP U/L	BILI mg/dL	BUN mg/dL	CREA mg/dL	CHOL mg/dL
Male, Group V - 100 mg/kg - Day 29											
665752	TRACE	NONE	NONE	234	165	39.8	313	0.14	16	0.49	51
665753	TRACE	NONE	NONE	108	75	15.0	252	0.10	16	0.40	47
665754	TRACE	NONE	NONE	119	70	12.8	225	0.11	14	0.49	52
665755	TRACE	NONE	NONE	120	63	11.6	195	0.12	14	0.42	41
665756	TRACE	NONE	NONE	130	66	14.8	168	0.11	13	0.42	61
665757	TRACE	NONE	NONE	134	96	22.3	263	0.12	15	0.40	53
665758	NONE	NONE	NONE	155	132	38.1	198	0.12	17	0.36	51
665759	TRACE	NONE	NONE	144	103	15.5	164	0.13	15	0.35	40
665760	TRACE	NONE	NONE	198	147	24.1	227	0.14	12	0.45	56
665761	TRACE	TRACE	NONE	111	78	11.9	245	0.12	13	0.39	58
Male, Group VII - 1000 mg/kg - Day 29											
665762	SMALL	NONE	NONE	185	90	7.2	257	0.14	14	0.36	53
665763	TRACE	NONE	NONE	123	82	10.3	248	0.12	14	0.43	57
665764	TRACE	NONE	NONE	107	80	12.2	244	<0.10	15	0.42	66
665765	TRACE	NONE	NONE	135	98	15.6	338	0.15	16	0.44	55
665766	TRACE	NONE	NONE	150	112	19.2	338	0.15	13	0.38	67
665767	TRACE	NONE	NONE	123	88	16.5	206	<0.10	16	0.39	56
665768	TRACE	NONE	NONE	121	80	7.7	248	0.15	12	0.40	54
665769	SMALL	NONE	NONE	372	297	20.4	258	0.16	18	0.50	52
665770	NONE	NONE	NONE	139	99	19.2	363	0.14	17	0.40	46
665771	TRACE	NONE	NONE	111	87	10.2	244	0.10	13	0.36	60

Individual Clinical Chemistry Values

Animal Number	TRIG mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Male, Group I - 0 mg/kg - Day 29										
665732	23	85	6.6	4.3	2.3	10.8	8.2	148.3	6.29	103.2
665733	27	94	6.6	4.5	2.1	10.9	8.8	149.8	6.47	102.4
665734	25	85	6.7	4.1	2.6	10.9	8.5	150.4	6.08	103.0
665735	23	83	6.8	4.3	2.5	11.1	7.8	151.3	6.14	103.3
665736	52	96	6.9	4.6	2.3	11.3	8.5	151.8	6.13	102.8
665737	25	106	6.7	4.2	2.5	10.6	8.2	147.1	6.37	98.1
665738	20	91	6.2	4.0	2.2	9.9	7.4	148.4	5.84	101.9
665739	26	81	6.6	4.2	2.4	10.8	7.9	150.3	6.27	103.5
665740	36	98	6.6	4.1	2.5	10.9	8.1	150.9	5.86	101.9
665741	39	95	7.1	4.5	2.6	11.0	7.3	151.3	6.42	103.7
Male, Group III - 10 mg/kg - Day 29										
665742	54	100	6.6	4.1	2.5	10.5	7.5	149.4	5.91	102.1
665743	41	91	6.2	4.0	2.2	10.6	7.7	150.5	6.05	104.0
665744	50	111	6.7	4.2	2.5	10.8	7.4	148.7	5.31	99.4
665745	25	93	6.6	4.2	2.4	10.8	8.0	151.8	5.96	105.0
665746	44	86	6.4	4.3	2.1	11.3	8.4	152.9	6.06	105.4
665747	66	80	6.5	4.1	2.4	10.1	7.8	147.7	5.74	100.8
665748	28	89	6.8	4.5	2.3	10.7	7.4	149.4	5.93	101.8
665749	28	101	7.1	4.2	2.9	10.7	8.1	148.3	6.37	102.5
665750	33	97	7.0	4.2	2.8	11.3	8.0	149.4	6.80	101.6
665751	66	125	6.8	4.1	2.7	11.4	9.2	149.7	6.35	101.9

Individual Clinical Chemistry Values

Animal Number	TRIG mg/dL	GLUC mg/dL	TP g/dL	ALB g/dL	GLOB g/dL	CALC mg/dL	IPHS mg/dL	NA mmol/L	K mmol/L	CL mmol/L
Male, Group V - 100 mg/kg - Day 29										
665752	74	96	7.1	4.5	2.6	10.9	8.8	150.7	6.55	102.7
665753	42	88	6.4	4.0	2.4	10.7	7.9	150.1	6.23	104.6
665754	26	91	6.4	3.8	2.6	10.6	8.5	147.7	6.31	104.2
665755	38	98	6.5	4.3	2.2	10.9	7.8	149.3	6.64	105.4
665756	46	86	6.5	4.0	2.5	10.2	7.4	151.3	5.71	104.9
665757	65	114	6.6	4.1	2.5	10.1	7.7	147.5	5.82	100.4
665758	42	88	6.4	4.0	2.4	10.4	7.8	149.5	5.65	102.5
665759	38	101	6.2	4.0	2.2	10.4	7.2	150.0	6.11	104.6
665760	49	109	6.6	4.2	2.4	10.7	7.8	150.7	6.44	104.6
665761	32	103	6.4	4.0	2.4	10.2	7.8	150.1	6.75	104.6
Male, Group VII - 1000 mg/kg - Day 29										
665762	40	85	6.7	4.2	2.5	10.0	8.1	149.2	6.66	102.4
665763	72	100	6.5	4.1	2.4	10.7	8.2	147.1	5.96	101.2
665764	46	106	6.4	3.9	2.5	10.6	8.0	147.8	5.75	101.8
665765	50	88	6.5	4.1	2.4	10.6	8.1	150.9	6.05	104.9
665766	103	105	6.8	4.1	2.7	10.6	8.6	150.8	5.84	103.3
665767	50	101	6.6	4.0	2.6	10.4	8.1	148.0	6.12	101.1
665768	44	100	6.8	4.0	2.8	10.6	7.8	148.7	5.41	101.9
665769	53	117	6.7	4.2	2.5	10.4	7.6	147.4	6.21	101.0
665770	54	95	6.9	4.3	2.6	10.9	8.3	149.7	5.92	102.8
665771	43	111	6.6	4.2	2.4	10.6	7.1	150.2	5.93	104.6

Individual Clinical Chemistry Values

Animal Number	PHEM	PLIP	PICT	PFLU µg/mL
Male, Group I - 0 mg/kg - Day 29				
665732	NONE	NONE	NONE	0.1
665733	NONE	NONE	NONE	0.1
665734	NONE	NONE	NONE	0.1
665735	NONE	NONE	NONE	0.1
665736	NONE	NONE	NONE	0.1
665737	NONE	NONE	NONE	0.1
665738	NONE	NONE	NONE	0.1
665739	NONE	NONE	NONE	0.1
665740	NONE	NONE	NONE	0.1
665741	NONE	NONE	NONE	0.1
Male, Group III - 10 mg/kg - Day 29				
665742	NONE	NONE	NONE	0.1
665743	NONE	NONE	NONE	0.1
665744	NONE	NONE	NONE	0.1
665745	NONE	NONE	NONE	0.1
665746	NONE	NONE	NONE	0.1
665747	NONE	NONE	NONE	0.1
665748	NONE	NONE	NONE	0.1
665749	NONE	NONE	NONE	0.1
665750	NONE	NONE	NONE	0.1
665751	NONE	NONE	NONE	0.1

Individual Clinical Chemistry Values

Animal Number	PHEM	PLIP	PICT	PFLU µg/mL
Male, Group V - 100 mg/kg - Day 29				
665752	NONE	NONE	NONE	0.1
665753	NONE	NONE	NONE	0.1
665754	NONE	NONE	NONE	0.1
665755	NONE	NONE	NONE	0.1
665756	NONE	NONE	NONE	0.1
665757	NONE	NONE	NONE	0.0
665758	NONE	NONE	NONE	0.1
665759	NONE	NONE	NONE	0.1
665760	NONE	NONE	NONE	0.1
665761	NONE	NONE	NONE	0.1
Male, Group VII - 1000 mg/kg - Day 29				
665762	NONE	NONE	NONE	0.1
665763	NONE	NONE	NONE	0.1
665764	NONE	NONE	NONE	0.1
665765	NONE	NONE	NONE	0.1
665766	NONE	NONE	NONE	0.1
665767	NONE	NONE	NONE	0.1
665768	NONE	NONE	NONE	0.1
665769	NONE	NONE	NONE	0.1
665770	NONE	NONE	NONE	0.1
665771	NONE	NONE	NONE	0.1

Individual Urinalysis Values

Animal Number	QUAL	COL	CLAR	VOL mL	UOSM mOsm/kg	pH	UGLU mg/dL	KET mg/dL	UBIL	BLD	URO EU/dL
Male, Group I - 0 mg/kg - Day 29											
665732	MEDIUM	YELLOW	CLEAR	3.8	2055	6.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665733	MEDIUM	YELLOW	CLEAR	5.0	1784	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665734	LIGHT	YELLOW	CLEAR	7.0	1189	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665735	LIGHT	YELLOW	CLEAR	10.4	937	6.5	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2
665736	LIGHT	YELLOW	HAZY	5.4	1590	6.5	NEGATIVE	5	NEGATIVE	TRACE	0.2
665737	LIGHT	YELLOW	HAZY	13.6	828	7.0	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2
665738	MEDIUM	YELLOW	CLEAR	2.2	3706	7.0	NEGATIVE	5	SMALL	NEGATIVE	1.0
665739	LIGHT	YELLOW	HAZY	28.0	412	7.0	NEGATIVE	NEGATIVE	NEGATIVE	TRACE	0.2
665740	LIGHT	YELLOW	HAZY	6.4	1347	7.0	NEGATIVE	15	NEGATIVE	NEGATIVE	0.2
665741	LIGHT	YELLOW	CLEAR	3.8	1663	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
Male, Group III - 10 mg/kg - Day 29											
665742	MEDIUM	YELLOW	HAZY	5.4	1653	6.5	NEGATIVE	15	NEGATIVE	TRACE	0.2
665743	LIGHT	YELLOW	CLEAR	10.4	761	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665744	LIGHT	YELLOW	HAZY	5.2	1949	6.5	NEGATIVE	15	NEGATIVE	TRACE	0.2
665745	LIGHT	YELLOW	HAZY	10.8	861	7.0	NEGATIVE	15	NEGATIVE	SMALL	0.2
665746	LIGHT	YELLOW	HAZY	6.0	1364	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665747	LIGHT	YELLOW	CLEAR	27.0	443	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665748	LIGHT	YELLOW	HAZY	8.0	991	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665749	LIGHT	YELLOW	HAZY	10.4	1112	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665750	LIGHT	YELLOW	CLEAR	10.6	1218	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665751	LIGHT	YELLOW	HAZY	8.0	1999	8.5	NEGATIVE	15	NEGATIVE	NEGATIVE	0.2

Individual Urinalysis Values

Animal Number	QUAL	COL	CLAR	VOL mL	UOSM mOsm/kg	pH	UGLU mg/dL	KET mg/dL	UBIL	BLD	URO EU/dL
Male, Group V - 100 mg/kg - Day 29											
665752	LIGHT	YELLOW	CLEAR	12.0	758	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665753	LIGHT	YELLOW	CLOUDY	4.6	1509	7.0	NEGATIVE	5	NEGATIVE	SMALL	0.2
665754	LIGHT	YELLOW	CLEAR	5.8	1550	7.0	NEGATIVE	15	NEGATIVE	NEGATIVE	0.2
665755	LIGHT	YELLOW	HAZY	6.8	1589	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665756	LIGHT	YELLOW	CLEAR	6.8	1176	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665757	MEDIUM	YELLOW	CLEAR	5.8	1307	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665758	MEDIUM	YELLOW	CLEAR	3.0	1802	7.0	NEGATIVE	15	NEGATIVE	NEGATIVE	0.2
665759	LIGHT	YELLOW	HAZY	7.0	1101	NT	NT	NT	NT	NT	NT
665760	LIGHT	YELLOW	HAZY	16.4	912	8.0	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	0.2
665761	LIGHT	YELLOW	HAZY	9.0	1123	8.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
Male, Group VII - 1000 mg/kg - Day 29											
665762	LIGHT	YELLOW	CLEAR	12.8	779	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665763	LIGHT	YELLOW	CLEAR	11.0	1107	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665764	LIGHT	YELLOW	CLEAR	8.8	888	6.5	NEGATIVE	5	NEGATIVE	TRACE	0.2
665765	LIGHT	YELLOW	HAZY	11.4	739	6.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665766	LIGHT	YELLOW	CLEAR	16.4	722	6.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665767	LIGHT	YELLOW	CLEAR	6.6	1080	6.5	NEGATIVE	5	NEGATIVE	MODERATE	0.2
665768	LIGHT	YELLOW	CLEAR	15.8	743	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665769	LIGHT	YELLOW	HAZY	8.0	1640	7.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665770	LIGHT	YELLOW	CLEAR	9.2	821	7.0	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2
665771	LIGHT	YELLOW	HAZY	8.2	1096	7.5	NEGATIVE	5	NEGATIVE	NEGATIVE	0.2

Individual Urinalysis Values

Animal Number	UFLU µg	UMTP mg/dL
Male, Group I - 0 mg/kg - Day 29		
665732	11.4	40
665733	15.3	159
665734	12.3	13
665735	15.2	69
665736	13.3	165
665737	20.7	190
665738	QNS	192
665739	21.7	84
665740	13.5	51
665741	10.2	151
Male, Group III - 10 mg/kg - Day 29		
665742	15.7	12
665743	18.2	48
665744	14.7	49
665745	14.4	60
665746	13.5	86
665747	23.2	95
665748	12.6	40
665749	15.5	81
665750	20.5	34
665751	25.4	94

Individual Urinalysis Values

Animal Number	UFLU µg	UMTP mg/dL
Male, Group V - 100 mg/kg - Day 29		
665752	19.1	110
665753	16.2	132
665754	23.5	29
665755	21.7	24
665756	21.0	29
665757	15.0	28
665758	11.0	84
665759	15.1	70
665760	29.7	64
665761	19.7	40
Male, Group VII - 1000 mg/kg - Day 29		
665762	35.8	52
665763	32.8	28
665764	27.5	34
665765	31.4	31
665766	44.9	47
665767	26.9	39
665768	61.8	32
665769	17.3	37
665770	27.6	20
665771	32.8	16

Individual Urine Microscopic Values

Animal Number	EPIT	UWBC	URBC	NCRY	MICR	SPER
Male, Group I - 0 mg/kg - Day 29						
665732	FEW	NONE	NONE	FEW	FEW	FEW
665733	NONE	NONE	NONE	FEW	FEW	MODERATE
665734	NONE	NONE	NONE	FEW	FEW	FEW
665735	FEW	NONE	NONE	FEW	FEW	MANY
665736	NONE	NONE	FEW	FEW	FEW	FEW
665737	NONE	NONE	NONE	FEW	FEW	MANY
665738	QNS	NT	NT	NT	NT	NT
665739	NONE	NONE	NONE	FEW	FEW	FEW
665740	NONE	NONE	NONE	MODERATE	FEW	MANY
665741	NONE	NONE	NONE	FEW	FEW	FEW
Male, Group III - 10 mg/kg - Day 29						
665742	FEW	NONE	NONE	FEW	FEW	FEW
665743	NONE	NONE	NONE	FEW	FEW	MODERATE
665744	NONE	NONE	NONE	FEW	FEW	FEW
665745	NONE	NONE	NONE	FEW	MODERATE	FEW
665746	NONE	NONE	NONE	FEW	FEW	MODERATE
665747	NONE	NONE	NONE	FEW	FEW	FEW
665748	NONE	NONE	NONE	FEW	FEW	FEW
665749	NONE	NONE	NONE	FEW	FEW	MODERATE
665750	NONE	NONE	NONE	FEW	FEW	MODERATE
665751	NONE	NONE	NONE	MODERATE	FEW	MANY

Individual Urine Microscopic Values

Animal Number	EPIT	UWBC	URBC	NCRY	MICR	SPER
Male, Group V - 100 mg/kg - Day 29						
665752	NONE	NONE	NONE	FEW	FEW	FEW
665753	NONE	NONE	NONE	FEW	FEW	FEW
665754	NONE	NONE	NONE	FEW	FEW	FEW
665755	NONE	NONE	NONE	FEW	FEW	MODERATE
665756	NONE	NONE	NONE	FEW	FEW	MODERATE
665757	NONE	NONE	NONE	FEW	FEW	FEW
665758	QNS	NT	NT	NT	NT	NT
665759	NONE	NONE	NONE	MODERATE	FEW	MODERATE
665760	NONE	NONE	NONE	FEW	MODERATE	MANY
665761	NONE	NONE	NONE	FEW	MANY	MANY
Male, Group VII - 1000 mg/kg - Day 29						
665762	NONE	NONE	NONE	FEW	FEW	MANY
665763	NONE	NONE	NONE	FEW	FEW	FEW
665764	NONE	NONE	NONE	FEW	FEW	MANY
665765	NONE	NONE	NONE	FEW	FEW	MODERATE
665766	NONE	NONE	NONE	FEW	FEW	FEW
665767	NONE	NONE	NONE	FEW	FEW	FEW
665768	NONE	NONE	NONE	FEW	MODERATE	MODERATE
665769	NONE	NONE	NONE	FEW	FEW	MANY
665770	NONE	NONE	NONE	FEW	FEW	MODERATE
665771	NONE	NONE	NONE	FEW	FEW	MANY

APPENDIX I

Individual Animal Final Body and Organ Weights

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS

Group : I 0 mg/kg Sex :MALES

ANIMAL	FBW (Gms)	KIDNEYS (Gms)	KIDNEYS %FBW	LIVER (Gms)	LIVER %FBW	THYROID GLAND (Gms)	THYROID GLAND %FBW
665732	367.10	3.603	0.9815	13.370	3.6421	0.022	0.0060
665733	374.40	3.391	0.9057	11.858	3.1672	0.014	0.0037
665734	344.90	3.056	0.8861	11.177	3.2406	0.017	0.0049
665735	325.60	2.757	0.8467	9.469	2.9082	0.015	0.0046
665736	349.80	2.764	0.7902	10.941	3.1278	0.018	0.0051
665737	NW	2.972		11.468		0.014	
665738	308.50	2.499	0.8100	9.907	3.2113	0.021	0.0068
665739	369.40	3.079	0.8335	10.394	2.8138	0.013	0.0035
665740	366.90	3.577	0.9749	10.330	2.8155	0.019	0.0052
665741	322.00	2.443	0.7587	9.029	2.8040	NW	
Mean	347.62	3.014	0.8653	10.794	3.0812	0.017	0.0050
S.D.	24.048	0.413	0.0783	1.266	0.2774	0.003	0.0011

NW = Not weighed due to technician error

FBW - Final Body Weight

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS

Group : III 10 mg/kg Sex :MALES

ANIMAL	FBW (Gms)	KIDNEYS (Gms)	KIDNEYS %FBW	LIVER (Gms)	LIVER %FBW	THYROID GLAND (Gms)	THYROID GLAND %FBW
665742	357.60	3.220	0.9004	11.866	3.3182	0.012	0.0034
665743	323.20	2.747	0.8499	9.521	2.9459	0.022	0.0068
665744	358.50	3.332	0.9294	10.955	3.0558	0.014	0.0039
665745	379.60	3.207	0.8448	10.301	2.7136	0.024	0.0063
665746	365.60	3.055	0.8356	10.983	3.0041	0.021	0.0057
665747	379.80	3.138	0.8262	10.959	2.8855	0.026	0.0068
665748	321.70	2.769	0.8607	9.960	3.0961	0.019	0.0059
665749	357.50	2.811	0.7863	9.900	2.7692	0.020	0.0056
665750	400.10	3.238	0.8093	12.686	3.1707	0.017	0.0042
665751	434.10	3.857	0.8885	13.914	3.2053	0.021	0.0048
Mean	367.77	3.137	0.8531	11.105	3.0164	0.020	0.0054
S.D.	33.563	0.330	0.0433	1.372	0.1925	0.004	0.0012

FBW - Final Body Weight

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS

Group : V 100 mg/kg Sex :MALES

ANIMAL	FBW (Gms)	KIDNEYS (Gms)	KIDNEYS %FBW	LIVER (Gms)	LIVER %FBW	THYROID GLAND (Gms)	THYROID GLAND %FBW
665752	349.00	3.050	0.8739	10.923	3.1298	0.020	0.0057
665753	333.10	2.641	0.7929	10.373	3.1141	0.015	0.0045
665754	386.20	3.271	0.8470	11.874	3.0746	0.016	0.0041
665755	352.10	2.845	0.8080	10.946	3.1088	0.017	0.0048
665756	336.40	2.565	0.7625	9.508	2.8264	0.015	0.0045
665757	331.00	2.764	0.8350	9.854	2.9770	0.017	0.0051
665758	347.10	3.260	0.9392	10.333	2.9770	0.019	0.0055
665759	330.00	2.966	0.8988	10.224	3.0982	0.016	0.0048
665760	348.30	3.298	0.9469	10.415	2.9902	0.017	0.0049
665761	307.10	2.487	0.8098	8.072	2.6285	0.018	0.0059
Mean	342.03	2.915	0.8514	10.252	2.9925	0.017	0.0050
S.D.	20.450	0.302	0.0622	1.004	0.1583	0.002	0.0006

FBW - Final Body Weight

INDIVIDUAL ANIMAL FINAL BODY AND ORGAN WEIGHTS

Group : VII 1000 mg/kg Sex :MALES

ANIMAL	FBW (Gms)	KIDNEYS (Gms)	KIDNEYS %FBW	LIVER (Gms)	LIVER %FBW	THYROID GLAND (Gms)	THYROID GLAND %FBW
665762	321.80	3.036	0.9434	10.006	3.1094	0.020	0.0062
665763	377.80	2.988	0.7909	11.661	3.0866	0.019	0.0050
665764	355.20	2.878	0.8102	11.442	3.2213	0.016	0.0045
665765	362.00	2.911	0.8041	10.613	2.9318	0.015	0.0041
665766	388.90	3.516	0.9041	14.101	3.6259	0.022	0.0057
665767	324.90	2.918	0.8981	10.549	3.2468	0.014	0.0043
665768	385.40	3.143	0.8155	11.865	3.0786	0.017	0.0044
665769	357.70	2.831	0.7914	10.642	2.9751	0.018	0.0050
665770	373.70	3.813	1.0203	12.746	3.4108	0.019	0.0051
665771	331.40	3.018	0.9107	12.111	3.6545	0.017	0.0051
Mean	357.88	3.105	0.8689	11.574	3.2341	0.018	0.0050
S.D.	24.679	0.316	0.0781	1.223	0.2542	0.002	0.0006

FBW - Final Body Weight

APPENDIX J

Individual Animal Pathology Data

INDIVIDUAL ANIMAL PATHOLOGY DATA

KEY TO APPENDIX

LESION GRADING:

Histopathology changes are described according to their morphologic character, distribution and severity. The distribution (extent of tissue involvement) is indicated, where appropriate, by modifiers such as focal, multifocal, diffuse, unilateral, bilateral, etc. A severity score, if appropriate, is also assigned as follows:

MINIMAL: The amount of change present barely exceeds that which is considered to be within normal limits.

MILD: In general, the lesion is easily identified but of limited severity. The lesion probably does not produce any functional impairment.

MODERATE: The lesion is prominent but there is significant potential for increased severity. Limited tissue or organ dysfunction is possible.

SEVERE: The degree of change is either as complete as considered possible or great enough in intensity or extent to expect significant tissue or organ dysfunction.

COMMENT:

Grades minimal through severe represent progressive involvement/severity along a continuum with minimal lesions being the least severe and severe lesions being the most severe. While the grades refer to the morphologic characteristics of lesions, they also indicate their relative biologic significance.

Gross observations listing multiple masses for a tissue are distinguished with letters (i.e., A, b, c, d, etc.).

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665732	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.

No Microscopic Abnormality Observed :
KIDNEYS, THYROID GLAND, SKIN, TEETH

665733	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
KIDNEYS :
NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.

665733 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665733	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : THYROID GLAND, SKIN, TEETH
665734	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal. HEMATOPOIESIS, EXTRAMEDULLARY, minimal. KIDNEYS : NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed : THYROID GLAND, SKIN, TEETH
665735	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

665735 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665735	Continued from previous page
	Histopathology :
	LIVER :
	HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
	No Microscopic Abnormality Observed :
	KIDNEYS, THYROID GLAND, SKIN, TEETH
665736	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER :
	HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	KIDNEYS :
	NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed :
	THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665737	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	No Microscopic Abnormality Observed : KIDNEYS, THYROID GLAND, SKIN, TEETH
665738	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.

665738 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665738	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : KIDNEYS, THYROID GLAND, SKIN, TEETH
665739	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : MACROPHAGES, PIGMENTED, FOCAL, minimal. HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal. KIDNEYS : NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed : THYROID GLAND, SKIN, TEETH
665740	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

665740 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : I 0 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665740	Continued from previous page

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
KIDNEYS :
NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.

No Microscopic Abnormality Observed :
THYROID GLAND, SKIN, TEETH

665741 Terminal Sacrifice
Killed on Day : 29
Animal is signed off from necropsy

Gross Pathology :

No Macroscopic Abnormality Observed :
LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Histopathology :

LIVER :
HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.

No Microscopic Abnormality Observed :
KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : III 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665742	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665743	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665744	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665745	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : III 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665746	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665747	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665748	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665749	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology : No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : III 10 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665750	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665751	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : V 100 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665752	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665753	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665754	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	TESTES : LARGE, BILATERAL, mild.
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

665754 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : V 100 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665754	Continued from previous page
	Histopathology :
	TESTES :
	NO MICROSCOPIC EVIDENCE OF MACROSCOPIC FINDING.
	No Microscopic Abnormality Observed :
	TESTES
665755	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665756	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665757	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : V 100 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665758	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665759	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
665760	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	KIDNEYS : DILATATION, UNILATERAL.
	No Macroscopic Abnormality Observed : LIVER, THYROID GLAND, SKIN, TEETH

665760 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : V 100 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665760	Continued from previous page
	Histopathology :
	KIDNEYS :
	DILATATION, PELVIS, UNILATERAL, mild.
665761	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665762	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
	No Microscopic Abnormality Observed : KIDNEYS, THYROID GLAND, SKIN, TEETH
665763	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.

665763 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665763	Continued from previous page
	Histopathology :
	KIDNEYS :
	NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed :
	THYROID GLAND, SKIN, TEETH
665764	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER :
	HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
	KIDNEYS :
	NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed :
	THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665765	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	No Microscopic Abnormality Observed : KIDNEYS, THYROID GLAND, SKIN, TEETH
665766	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. KIDNEYS : NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.

665766 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665766	Continued from previous page
	Histopathology :
	No Microscopic Abnormality Observed : THYROID GLAND, SKIN, TEETH
665767	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal. TEETH : HEMORRHAGE, mild, peridontal . INFLAMMATION, ACUTE, mild, peridontal .
	No Microscopic Abnormality Observed : KIDNEYS, THYROID GLAND, SKIN
665768	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH

665768 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665768	Continued from previous page
	Histopathology :
	LIVER :
	HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
	No Microscopic Abnormality Observed :
	KIDNEYS, THYROID GLAND, SKIN, TEETH
665769	Terminal Sacrifice
	Killed on Day : 29
	Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed :
	LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER :
	HEMATOPOIESIS, EXTRAMEDULLARY, minimal.
	INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
	NECROSIS, HEPATOCELLULAR, FOCAL, minimal.
	KIDNEYS :
	NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed :
	THYROID GLAND, SKIN, TEETH

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665770	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal. INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal. KIDNEYS : NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.
	No Microscopic Abnormality Observed : THYROID GLAND, SKIN, TEETH
665771	Terminal Sacrifice Killed on Day : 29 Animal is signed off from necropsy
	Gross Pathology :
	No Macroscopic Abnormality Observed : LIVER, KIDNEYS, THYROID GLAND, SKIN, TEETH
	Histopathology :
	LIVER : HEMATOPOIESIS, EXTRAMEDULLARY, minimal.

665771 Continued on the next page ....

Individual Animal Pathology Data

Dose Group : VII 1000 mg/kg Sex: Males

Animal Ref	Microscopic & Macroscopic Findings
665771	Continued from previous page

Histopathology :

LIVER :
INFLAMMATION, SUBACUTE/CHRONIC, FOCAL, minimal.
KIDNEYS :
NEPHROPATHY, CHRONIC PROGRESSIVE, minimal.

No Microscopic Abnormality Observed :
THYROID GLAND, SKIN, TEETH